



# THE PRACTICE OF MEDICINE





# THE PRACTICE OF MEDICINE

BY

**JONATHAN CAMPBELL MEAKINS, CBE, MD, LL.D., D.Sc.**

Formerly Professor of Medicine and Director of the Department of Medicine McGill  
University Formerly Physician in Chief Royal Victoria Hospital Montreal Formerly  
Professor of Therapeutics and Clinical Medicine University of Edinburgh  
Fellow of the Royal Society of Edinburgh Fellow of the Royal Society of  
Canada Fellow of the Royal College of Physicians London Fellow  
of the Royal College of Physicians Edinburgh Honorary  
Fellow of the Royal College of Surgeons Edinburgh  
Fellow of the Royal College of Physicians  
Canada Fellow of the American College of  
Physicians Honorary Fellow of the  
Royal Society of Medicine

**FIFTH EDITION**

**WITH 518 ILLUSTRATIONS INCLUDING 50 IN COLOUR**

LONDON  
HENRY KIMPTON

1950



TO  
MY WIFE  
SARA CALDWELL MEAKINS

THIS BOOK IS  
AFFECTIONATELY DEDICATED



## PREFACE TO FIFTH EDITION

The task of writing a new edition of *The Practice of Medicine* is becoming increasingly difficult. This is so for a number of reasons of which the most specific is the upsurge of specialized techniques. In other words the wide view of medicine is being clouded by a multiplicity of minutiae which are beyond the technical capacity or facilities of the general physician. Indeed the requirements of medical practice are becoming so complicated that there must be in the near future if not immediately some organized effort to bring these diagnostic and therapeutic facilities to the doctor and the patient. This general absence however does not afford an excuse for neglecting to include or even emphasize them in the present text. The fortunate patients who have access to metropolitan clinics have these facilities readily available. However they make up a comparatively small percentage of those who suffer from ill health. Furthermore human disabilities do not in the main come from rare or exotic diseases but are due to more obvious and too often neglected causes such as economic, social and emotional situations.

If one reviews the progress of medicine over the past three generations it becomes increasingly apparent that a logical but not always necessarily a connected developmental progression has occurred. The great school of pathological anatomy led by Virchow pointed the way to a basic concept of disease. The almost coincident concept of microscopic agents causing many of these anatomical changes was placed on a firm foundation by Lister, Lister and Koch. The progress of bacteriology found gaps in the explanation of many infectious diseases and so in time the role of rickettsiae, viruses, protozoa and other agents was authenticated. Medicine now had a concrete problem to solve, namely the search for specific methods of protection against or antagonists to these agents. So were born the modern methods of protective inoculation and chemotherapy. But medical thought in the meantime had also been concentrated upon disturbances of function or what today we are inclined to call pathologic or abnormal physiology. It was a belated but obvious progression from the school of pathological anatomy. In other words the experimental method was again introduced. On this was developed the concept of physiological deficiencies and excesses and other perversions of function. It was but a short step to link these with anatomical abnormalities. But this was not always successful and so there still remain gaps in our complete knowledge. For example why diabetes mellitus? It is held to be due to a primary defect of the islands of Langerhans. But the evidence is not always one might even say it is seldom conclusive.

It was a natural progression in physiology that biochemical and biophysical techniques should steadily become important and even fundamental frontiers in the elucidation of abnormal processes. So now the biochemist, sterol chemist, colloid chemist, enzymologist, biophysicist (including experts in atomic energy research), parasitologist, protozoologist, epidemiologist, mathe-

matrician and many other specialists dealing with man as an organic animal are focusing their spotlights on his physical defects. This is as it should be but sometimes enthusiastic hypothesis based upon a modicum of fact has far outstripped reason. This has not been kept within rational practice by the many uncontrolled publications in the professional as well as the lay press.

During many of these decades man was mostly concerned with man as a biological specimen rather than as a loving, hating, propagating, thinking, complete unit. In fact most physicians relegated the emotional difficulties to their "nerves" or some other equally disparaging term. It must be conceded that the older physician was an unconscious psychologist but for a long period the advances of medicine did not leave room for any concept which could not be measured by a formula or in milligrams. This is not intended as an indictment but simply a fact in the progress of medical thought. The blame for this point of view might with justice be laid at the door of the psychiatrists. There was not much difference between the mental outlook of the therapeutic nihilist of 1900 and that of the average psychiatrist of 1925. There were however as always a few far-seeing men who could not accept this fatalism. These were not confined within the discipline of psychiatry but within their numbers there were psychologists, sociologists, economists, educationalists, anthropologists, philosophers, statesmen, labor leaders, industrialists and others. The dignity of man in his social, economic and emotional environment was their concern. They did not deny that a physically healthy body was a just and reasonable requirement but this was of little avail if the spirit and mind were in travail. So there gradually evolved a more realistic concept of disease as a whole. Psychiatry took to itself a more comprehensive place in medicine. The interactions of psychology, physiology, biochemistry, endocrinology and even ultimate effects upon anatomical structure are now being appreciated and are taking their places in the understanding of all health.

In the present edition it has seemed advisable to remove the sparse section on psychiatry and to replace it with one on psychosomatic medicine. There is a large body of opinion which takes exception to this term but it must remain until someone has the ingenuity which this writer has not to coin a better one. This task has been undertaken by Dr. Frederick R. Hanson to whom I express my sincere thanks.

The chapter on the nervous system has been maintained for several reasons. As a classical description of neurological lesions it has few if any equals for a text of this character. It was the creation of a great neurologist, Dr. J. N. Petersen, whose death at an early age was a great loss to the medical science and to a host of devoted friends among whom this author was proud to be numbered.

The rapid advance in chemotherapy and antibiotics has in a way simplified the treatment of infections but it has also somewhat complicated the description thereof. In order to reduce reduplication a chapter has been devoted to this subject. In this has been condensed the principles of chemotherapy and antibiotics and the indications and manner of their use. It is hoped that by this

means a clearer understanding may be obtained upon which further advances may rest. New discoveries are almost monthly events but the fundamental principles remain unchanged.

In all the chapters a valiant attempt has been made to bring them up to date but with the tempo of the times this is a difficult task. Seeming sins of omission have occurred on purpose as it was felt that their validity was not sufficiently proved to warrant their inclusion. For this we make no apologies.

The chapter on the ductless glands has been largely rewritten. An attempt has been made to clarify the classical description of some of the diseases of these organs in order that it may be appreciated that there are quantitative and qualitative variations in their functions and that their interrelationships cannot be ignored or neglected.

In conclusion I wish to renew my thanks to my colleagues Dr F. H. Mason and Dr Walter deM. Sriver for their continued assistance and cooperation. Also I would desire to thank Dr Martin Hoffman for many helpful suggestions and timely criticisms.

JONATHAN C. MEAKINS

Montreal, Canada



## PREFACE TO THE FIRST EDITION

It would seem audacious for one to attempt to write a treatise on the practice of medicine at this time when specialization has become so highly developed. This volume is not intended for the specialist, nor does it aspire to be encyclopedic, but rather for the student and practitioner, to assist them in solving the numerous puzzles and problems with which they are daily confronted. So far as the patient is concerned, disease consists of symptoms. It is for these that he or she consults a physician. They represent the earliest manifestations of disease and therefore are of primary importance. They are the clues to the clinical riddles. For this reason they have been given particular prominence and where possible their causation has been described and their significance has been pointed out.

This is a pictorial age and many factual data are capable of graphic records. Therefore I have departed from the usual custom in textbooks on the practice of medicine and have inserted many illustrations with the hope that these may be more informative than a word description. I have kept before my mind the fact that the patient presents symptoms and signs which indicate disturbances of function and from these the pathological conditions may be traced and identified. It has been my hope that this book would be a guide to the practice of medicine as well as a description of individual diseases.

I am particularly indebted to my colleagues for their contributions, Dr E. H. Mason for the chapters on Diseases of Metabolism and Diseases of the Ductless Glands, Dr Walter deM. Sriver for the chapter on Diseases of the Urinary System and Dr J. Norman Petersen for the chapter on Diseases of the Nervous System. I also wish to express my thanks to Dr J. S. L. Browne and Dr David L. Thomson for help and advice especially in matters of the ductless glands. To both authors and publishers who have so generously assisted by permitting the use of their published illustrations I wish to express my sincere thanks. Figs 456 483-487 490 492 are reproduced from the Army Medical Bulletin No 1 January 1913 Photomicrographs of Spirochetes Entamoebae, Plasmodia Trypanosomes Leishmania Negri Bodies and Parasitic Helminths by permission of The Surgeon General of the United States. To my secretaries Miss M. R. Imrie and Miss V. L. Davidson I am indebted for their care and patience in preparation of the manuscript, and to my librarian Miss Genevieve Dunne for the verification of the references.

JONATHAN MEAKINS

Montreal Canada

# CONTENTS

## CHAPTER I

### AN INTRODUCTION TO THE PRACTICE OF MEDICINE

PAGE

1

The Approach to the Patient 3 Symptomatology 7 Etiological Factors in Disease 10 Diagnosis of Disease 16 Treatment of Disease 17

## CHAPTER II

### DISEASES OF THE NASOPHARYNX AND MOUTH

19

Introduction 19 Diseases of the Nose 20 Acute Rhinitis 20 Hypertrophic Rhinitis 21 Chronic Rhinitis 21 Atrophic Rhinitis 22 Rhinitis Sicca 3 Specific Infection 3 Secondary Lesion 24 Tumors 26 Diseases of the Pharynx 2 Acute Pharyngitis 2 Chronic Pharyngitis 2 Specific Infection 25 Herpetic Pharyngitis 25 Tumors of the Pharynx 26 Diseases of the Mouth 27 Congenital Anomalies 27 Diseases in Infancy 27 Diseases of Older Children and Adults 30 Diseases of the Tongue 3 Stomatitis 4 Ulcerative Stomatitis 4 Gangrenous Stomatitis 4 Disease of the Salivary Glands 40 Disturbances of Function 40 Acute Local Non-specific Stomatitis (Parotitis) 40 Chronic Parotitis 41 Calculi 47 Tumors 48

## CHAPTER III

### SYSTEMIC INFECTIONS OF THE NASOPHARYNX AND MOUTH

50

Tonsillitis 50 Acute Follicular Tonsillitis 50 Follicular Follicular Tonsillitis 51 Exudative Tonsillitis and Pharyngitis of Unknown Cause 51 Necrotic Tonsillitis 51 Chronic Tonsillitis 51 Acute Hemorrhagic Fever 51 Scarlet Fever 51 Diphtheria 52 Mumps 94 Measles 94 Typhoid 101 Influenza 106 Secondary Lesion 109 Bronchitis 109 Bronchiolitis and Bronchopneumonia 109 Paranasal Sinusitis 110 Otitis Media 110 Myelloma 111

## CHAPTER IV

### DISEASES OF THE LARYNX AND BRONCHIAL SYSTEM

115

Introduction 115 Symptomatology 115 Larynx 119 Functional Disorder 119 Paralysis 121 Inflammatory Lesion 12 Non-specific Infection 12 Specific Infection 14 Whooping Cough 14 Tuberculosis 149 Injury 150 Aphonia 150 Tumors 151 Trachea and Bronchi 152 Acute Tracheobronchitis 153 Acute Laryngotracheobronchitis 153 Respiratory Gas Poisoning 157 Myocarditis 157 Laryngitis 159 Laryngitis 160 Infective Causes 162 Tuberculous Tracheitis 163 Fibrous Bronchitis 163 Squamous Bronchitis 163 Chronic Bronchitis 163 Bronchiectasis 169 Cells of the Lung 169 New Growths of the Bronchi 169 Foreign Bodies 1

## CHAPTER V

### DISEASES OF THE LUNGS

118

Symptomatology 118 Cyanosis 119 Cyanosis in Clinical Conditions 119 Respiratory Disease 119 Laryngeal and Tracheal Obstruction 119 Acute Pulmonary Diseases 125 Chronic Pulmonary Diseases 125 Diseases of the Circulation 128 Physicochemical Condition 128 Dyspnea 128 Signs 129 Circulatory Disturbance 130 Hemorrhage 134 Pulmonary Infarction 134 Atelectasis 139 Acute Massive Pulmonary Collapse 202 Empyema 203 Bronchopneumonia 204 Friedlander Pneumonia 203 Pittacosis 204 Primary Atypical Pneumonia 205 Pneumonic Plague 206 Lobar Pneumonia 206 Chronic Pneumonitis, 205, Pneumoconiosis 271 Lipoid Pneumonia, 274

## CHAPTER VI

DISEASES OF THE LUNGS (Contd.)	PAGE
Infectious Granulomata 278 Introduction 278 Tuberculosis of the Lung 289	278
Clinical Forms and Course of Pulmonary Tuberculosis 29 Primary Infection, 29 Acute Miliary Tuberculosis 293, Chronic Miliary Pulmonary Tuberculosis 293 Chronic Fibroulcerative Pulmonary Tuberculosis 296 Acute Pneumonic Phthisis 299 Fibroid Tuberculosis 301 Complication of Pulmonary Tuberculosis 303, Pulmonary Tuberculosis and Silico 303, Extent of the Lesion, 306 Degree of Systemic Disturbance 306 Syphilis of the Lungs 313 Benign Lympho Granuloma 314 Mycotic Disease of the Lungs 317 Blastomycosis 318 Coccidioidomycosis 318 Cryptococcosis 319 Histoplasmosis 319 Actinomycosis 319 Monilia 320 Aspergilliosis 320 Liver Mycosis 321, Hydatid Disease of the Lung 321	

## CHAPTER VII

DISEASES OF THE CIRCULATORY SYSTEM	PAGE
Introduction 323 General Symptomatology 323 Circulatory Failure 324, Diseases of the Heart 324 Cardiac Arrest 324 Congestive Cardiac Failure 324 Peripheral Circulatory Failure 329 Neurocirculatory Asthenia 33, Valvulitis 373 Cardiac Enlargement 391 Peripheral Signs 392 Pulmonary Signs 393 Rhythmic Disturbances 394 Sinus Tachycardia 396 Sinus Bradycardia 396 Pathic Sinus Arrhythmia 396 Sinus Block 396 Auricular Premature Beat 398 Idioventricular Tachycardia 399 Auricular Flutter 399 Auricular Fibrillation 399 Atrioventricular Block 399 Bundle Branch Block 399 Atrioventricular Block 400 Ventricular Premature Contraction 400 Idioventricular Tachycardia 403 Myocardium 403 Pathological Anatomy 404 Lesion of the Endocardium 405 Acute and Subacute Bacterial Endocarditis 405 Subacute Bacterial Endocarditis 409 Streptococcal (Hemolyticus) Endocarditis 412, Influenzal Endocarditis 412 Pneumococcal Endocarditis 412, Gonococcal Endocarditis 413 Staphylococcal Endocarditis 414 Bacteriology 414 Pathological Anatomy 416 Congenital Heart Disease 421 Diseases of the Blood Vessels 421 Introduction 429 Diseases of the Aorta 431 Arteriovenous Aneurysm 442 Dissecting Aneurysm 443 Disturbance of Blood Flow 444 Periarthritis Nodosa 458 Local Peripheral Diseases 460 Erythromelalgia 462 Immersion Foot 463, Lavanula Disease 464 Aerobacteraemia 465 Thromboangitis Obliterans 466 Local Vascular Disease 470 Arteriosclerotic Vascular Disease 482 Syphilitic Cardiac Disease, 483 Diseases of the Pulmonary Arteries 484 Diseases of the Vein 485	321

## CHAPTER VIII

DISEASES OF THE SEROUS MEMBRANES, MEDIASTINUM AND DIAPHRAGM	PAGE
Introduction 490 Diseases of the Serous Cavities 492 Pleurisy 492 Pneumothorax 497 Pericarditis 499 Peritonitis 502, Chronic Adhesive Peritonitis 507 Disturbances of Circulation 509 Tumors of Serous Cavities 509 Diseases of the Mediastinum 509 Infections of the Mediastinum 509 Acute Mediastinal Emphysema 510 Tumors of the Mediastinum 511 Diseases of the Diaphragm 512 Inflammatory Lesion 51 Intercostal Muscle 51	490

## CHAPTER IX

DISEASES OF THE HEMATOPOIETIC SYSTEM	PAGE
Bone Marrow 520 Erythrocyte 521 Leucocyte 521 Hypochromic Microcytic Anemias 530 Chlorosis 530 Idiopathic Hypochromic Anemia 533 Hypochromic Anemia in Pregnancy 534 Nutritional Hypochromic Anemia, 535 Hyperchromic Macrocytic Anemias 537 Pernicious Anemia 537 Microcytic Hyperchromic Anemias 546 Aplastic Anemia 546 Sickle Cell Anemia 547 Chronic Hemolytic Jaundice, 549 Nonfamilial Hemolytic Jaundice 550 Poly	520

cytlemia Vera 51 Splenic Anemia 3 Diarrhea of the Large Intestine 3  
 Leukemia 3 Aleukemic Leukemia 3 Acute Leukemia 360 Menstrual  
 Leukemia 63 Echinophili Leukemia 361 Nutritional 361 Aggranulocytosis  
 361 Diarrhea of the Blood 361 Causes of Purpura 361 Thrombocyto-  
 penia 361 Hemophili 361 Erythral Purpura 361 Essential Thrombocythia  
 361 Diarrhea of the Spleen and Hematological System 364 The Spleen  
 364 Thrombocytoblastic System 364 Mucous Intestine 364 Large Cell  
 Splenomegaly (Cauliflower Spleen) 364 Splenic Infarction (Necrotic Splen-  
 itis) 364 Splenic Granuloma 364 Diarrhea of the Lymphatic System  
 Hodgkin's Disease 364 Lymphatic System 364

## CHAPTER 8

## DISEASES OF THE GASTROINTESTINAL TRACT

Diarrhea of the Esophagus 86 Hemorrhage of the Esophagus 86 Anemia 86 Traumatic Lesion 88 Inflammation 88 Stenosis of the Esophagus 90 Functional 90 Diverticulum of the Esophagus 93 Tumor of the Esophagus 94 Diverticulum of the Stomach 94 Intubation 98 Symptomatic 99 Functional Diarrhea 100 Gastric and Duodenal Ulcer 100 Syphilis of the Stomach 101 Tubercle of the Stomach 106 Tumor of the Stomach 11 Benign Tumors 11 Malignant Tumors 118 Gastritis 12 Acute Gastritis 12 Ate Suffering Gastritis 13 Chronic Gastritis 14 Gastric Neurosis 16 Gastric Alony 18 Intestinal Obstruction 18 Diverticulum of the Small Intestines 19 Functional 19 Diverticulum of the Duodenum 19 Duodenitis 19 Leptile Ulcer 19 Jejunal Ulcer or Marginal Ulcer 19 Duodenal Stenosis 19 Intestinal Diverticulum 19 Diseases of Intestinal Absorption 19 Enteric Stenosis 19 Stenosis of the Duodenum 19 Nutritional Syphilis 19 Tropical Syphilis 19 Malignant Stenosis 19 Diverticulum of the Large Intestines 19 Functional Diverticulum of the Colon 19 Mucocele 19 Appendicitis 19 Acute Appendicitis 19 Diverticulitis 19 Peritonitis 19 Tumor 19 Inflammatory Diverticulum of the Intestinal Tract 19 Acute Catarrhal Enteritis 19 Specific Enterocolitis 19 Infectious 19 Dysenteric Cramp 19 Anemia 19 Dysentery 19 Biliary Dysentery 19 Cholera 19 Jejunointestinal 19 Typhoid Colic 19 Typhoid Fever 19 Salmonella typhimurium Infection 19 Unilateral Fever 19 Chronic Intestinal Colitis 19 Intestinal Parasites 19 Nematode (Roundworm) Infection 19 Ascaris 19 Oxyuriasis 19 Ankylostomiasis 19 Trichocephalus 19 Trichuriasis 19 Trichinosis 19 Trichinosis 19 Cystic (Tapeworm) Infection 19 Taenia 19 Hymenophorus 19 Dipylidiosis 19 Dipylidiosis 19 Dipylidiosis 19 Dipylidiosis 19 Trematodes (Flukes) Infection 19 Schistosomiasis 19 Protozoan Intestinal Infection 19 Cystic 19 Balantidiosis 19

## CHAPTER XI

## DISEASES OF THE LIVER AND BILE PASSAGES

Introduction 15 Hepatic Circulation 15 Carbohydrate Metabolism 15 Protein Metabolism 22 Fat Metabolism 23 Mineral Metabolism 23 Bile Secretion 23 Detoxifying Function 24 Hematologic Function 24 Dye Tests of Hepatic Function 24 Diseases of the Liver 31 Anomalous 31 Hepatitis 31 Acute Infectious Hepatitis 31 Acute Suppurative Hepatitis 32 Yellow Liver 36 Acute Suppurative Hepatitis (Abscess) 39 Degenerative Lesions 39 Chemical Intoxication 39 Infective Hepatitis 40 Acute Yellow Atrophy 41 Subacute Hepatitis 44 Chronic Hepatitis 44 Syphilis of the Liver 50 Tumors of the Liver 51 Solid Tumor 51 Cystic Tumor 54 Secondary Hepatic Diseases 54 Diseases of the Gallbladder and Bile Passage 54 Introduction to the Gallbladder and Bile Passage 54

duction 754 Function, 755 Special Methods of Examination 755, Anomalous, 758, Biliary Obstruction 758 Diseases of the Gallbladder, 759 Inflammation, 759 Cholelithiasis, 760, Tumors of the Gallbladder, 767 Diseases of the Bile Ducts 768 Inflammations 768 Carcinoma of the Bile Duct 771 Diseases of the Pancreas 773, Acute Hemorrhagic Pancreatic Necrosis, 773 Chronic Pancreatitis 774 Tumors 775, Pancreatic Calculi 776

## CHAPTER VII

### DISEASES OF NUTRITION

Introduction 780 Starvation 780 Effect of Injury and Disease on Nutrition 781 Chronic Malnutrition, 782 Nutritional Defects 781, Avitaminosis 781, Vitamin A 784, Vitamin B 785 Beriberi 78 Subclinical Type 789, Pellagra 789 Secondary Pellagra 91 Aerobiosis 91 Vitamin C Deficiency 90, Scurvy 90 Subclinical Vitamin C Deficiency 99 Vitamin D 99 Rickets 99 Osteomalacia 803 Vitamin K 804 Vitamin I 805 Hypervitaminosis, 806

## CHAPTER VIII

### DISEASES OF METABOLISM

Introduction 809 Diabetes Mellitus 809 Complications, 810 Diagnosis 810 Prognosis 838 The Objectives and Principles of Treatment 819 The Low Fat High Carbohydrate Diet 841 The Treatment of Complications 846 The Use of Insulin 851 The Use of Drugs 854 Fasting and Carbohydrate Tolerance 854 The Diabetic Child 854 Diabetes and Pregnancy 856 Surgical Operations Upon Diabetes 857 The Introduction of the Diabetic 859 The New Diet 859 Hyperuricemia 858 Renal Glycosuria (Renal Diabetes) 860 Acid Base Balance 861 Acids 864 Alkalosis 866 Diabetes Insipidus 869 Cystitis 870 Otitis 871 Typhoid 883 Hemorrhoids 884 Otitis 885

## CHAPTER IX

### DISEASES OF THE DUCTLESS GLANDS

Introduction 888 Diseases of the Pituitary Gland 890 Introduction 890 Hypopituitary Function 892 Acromegaly 893 Basiophilism 896 Hypopituitary Function 897 Frohlich's Syndrome (Distrophic Adipogenitalis) 89 Simmonds Disease 899, Compression Syndromes 904 Craniopharyngioma 904 Chromophobe Adenoma 905 Dwarfism 906 Diseases of the Thyroid Gland 908 Introduction 908 Classification of Diseases of the Thyroid Gland 909 Adenomatous (Diffuse and Nodular) 909 Cystic-Nontoxic 911 Cystic-Toxic 913 Cystic-Fibrotic Diffuse and Nodular 914, Cystic Disease Below 914 Thyroiditis 921, Tumors of the Thyroid Gland 922 Myxedema 923 Cretinism 927 Developmental Anomalies 929 Hypometabolism Without Myxedema, 929 The Thyroid and Pregnancy 929 Diseases of the Suprarenal Glands 930 Introduction 930 Hypoadrenal Function 931 Acute Insufficiency of the Adrenal Cortical Function (Waterhouse-Friderichsen Syndrome) 933 Addison's Disease 934 Hyperadrenal Function 940 Tumors 940 Tumors of the Cortex 941 Tumors of the Medulla 943 Paraganglioma 943 Diseases of the Gonads 944 Introduction 944 Abnormalities of the Male Gonad 946 Abnormalities of the Female Gonad 951 Developmental Abnormalities 950 Diseases of the Parathyroid Glands 960 Introduction 960 Calcium Metabolism 960 Hypoparathyroid Function 961 Tetany (Sporadic) 961 Parathyroid Carcinoma, 964 Hyperparathyroidism (Osteitis Fibrosa Cystica) 964 Diseases of the Pineal Gland 966 Pineal Tumors 966, Diseases of the Thymus Gland 967 Thymus Tumors, 967 Status Thymicolymphaticus 969 Carotid Body (Carotid Glands and Carotid Sinus) 969, Tumors of the Carotid Gland, 971

## CHMTR: 25

### IN CASES OF THE SERVING SYSTEM

[illegible]

## CHEMICAL ANALYSIS

## ISYCHOSOMATIC METHOD 157

Introduction 1161 Psychological Considerations 116 Psychophysiological Mechanisms 1168 Organ Choice 116 General Consideration of Therapy 117 Psychotherapy 117 Systemic Considerations 117 Personality System 118 Cardiovascular System 118 Emotional Effects in the Normal Heart 119 Emotional Conflict and the Diseased Heart 119 Emotional Factors in Hypertension 118 Gastrointestinal System 119 Upper Gastrointestinal Tract 119 Lower Gastrointestinal Tract 119 Endocrine System and Metabolism 119 Locomotor System

CHAPTER XVII

DISEASES OF THE LOCOMOTOR SYSTEM

PAGE  
120

Introduction 120 Diseases of the Bone 120, Tumor 120, Multiple Myeloma 120b Metastatic Carcinoma 120c Metalloids and Developmental Disorder 120d Achondroplasia, 1210 Multiple Cartilaginous Exostoses, 1213 Multiple Congenital Endochondrosis 1214, Osteogenesis Imperfecta 1215, Osteopetrosis 1216 Fibrous Dysplasia 1219 Other Hereditary Bone Disease 1220 Hypertrophic Osteodystrophy 1220, Osteitis Deformans 1222 General Hyperkeratosis of the Skull 1227 Vertebrae 1227 Diseases of the Muscle 1229, Introduction 1229 Primary Suppurative Myositis 1230 Dermatomyositis 1231, Myositis Fibrosa (Myositis Chronica) 1232 Myositis Ossificans Traumatica 1233 Myalgia 1234 Bursitis 1234, Diseases of the Joints 1235, Introduction 1235 Septic Arthritis 1236 Chronic Non-suppurative Arthritis 1237 Rheumatoid Arthritis, 1238 Infectious Disease, 1240 Idiopathic Rheumatism, 1240, Osteoarthritis, 1240

CHAPTER XVIII

DISEASES OF THE URINARY SYSTEM

1250

Introduction 1250 Symptomatology 1257 Tests of Renal Function 1259 Bright Disease 1260 The Experimental Production of Nephritis 1261 Glomerulonephritis 1264 Acute Glomerulonephritis (Acute Hemorrhagic Nephritis) 1265 Chronic Glomerulonephritis, 1266, Nephroses 1269 The Urine Site, 1269 Symptom and Signs of Urinæ 1270 The Nephrotic Syndrome 1272, Interstitial Glomerulonephritis 1273 Vascular Renal Failure 1276 Treatment of Nephritis 1276 The Artificial Kidney 1281 London Lecture 1281, Orthostatic Albuminuria 1282 Amyloid Disease of the Kidney 1283 Congenital Polycystic Kidney 1283 Congenital Aplasia of the Kidney 1283 Renal Arteriosclerosis, 1284 Infarcts of the Kidney 1284 Lower Nephron Nephrosis 1284, Tubulovascular Renal Syndrome, 1284, Infections of the Kidney 1284, Nephrolithiasis (Renal Calculus) 1290 Hydronephrosis 1290 Tumor of the Kidney 1296

CHAPTER XIX

INFECTIOUS DISEASES

1297

Classification 1299 Septicemia 1300 Erysipelas 1304 Syphilis 1305 Congenital Syphilis 1310 Yaws 1314 Lymphopathia Venereum 1315 Cranioma Inguinal 1320 Gonorrhea 1329 Tularemia 1334 Anthrax 1335 Glanders 1339 Tetanus 1341 Foot and Mouth Disease 1344 Infections Due to the Bites of Mammals 1344 Injuries 1346 Rat Bite Fever 1347 Diseases Caused by Insect Bites, Ticks and Other Biting Insects 1349 Typhus Fever 1351 Tatsugamushi Disease 1354 Trench Fever 1355 Rocky Mountain Spotted Fever 1357 Relapsing Fever 1359 Malaria 1360 Q Fever 1364 Bull's Fever 1364 Colorado Tick Fever 1365 Tick-tail-pox 1365 Swineherd's Disease 1365 Diseases Caused by Blood-Sucking Insect 1366 Malarial Fevers 1366 Filariæ 1368 Filarial Lymphangitis 1379 Elephantiasis 1380 Dengue 1382, Japanese Fever 1383 Leishmaniasis 1384 Oriental Sore 1384 Spundri 1386 Kala-azar 1386 Trypanosomiasis 1389 African Sleeping Sickness 1390 Chagas Disease 1391 Infections With an Uncertain Portal of Entry 1392 Smallpox 1392 Chickenpox 1399 Herpes Zoster 1400 Lymphocytic Choriomeningitis 1401 Acute Mononucleosis 1402 Epidemic Pharyngitis 1403 Leprosy 1404 Toxoplasmosis 1409 Erythematous 1410 Iupus Erythematosus Diminutus 1411

CHAPTER XX

CHEMOTHERAPY AND ANTIBIOTICS

1419

Definition, 1419 Bacterial Effect 1420 Prerequisites for Therapy 1421 Solubility and Absorption 1422 Acetylation 1423 Distribution 1423 Excretion, 1423 Toxic Effects 1424 Method of Administration and Dosage 1426 Indications for Therapy 1429 Prophylaxis 1431 Curative Therapy, 1433

## CHAPTER XVI

PAGE

## DISEASES DUE TO ALLERGY

143

- Introduction 143: Serum Disease or Serum Sickness 143, Serum Shock 143  
 Allergy 144: Detection of Allergy 144: Urticaria 144: Hay Fever 144  
 Anaphylactic Phenomena (Serum Reaction) 146: Asthma 146: Gastrointestinal  
 Allergy 146: Physical Allergy 146: Latent and Hereditary Allergy 146: Miscellaneous Allergic Reactions 146

## CHAPTER XVII

## DISEASES DUE TO ABNORMAL PRESSURES

144

- Introduction 144: Effect of Height 144: Effect of Cold 146: Effect of High  
 Barometric Pressure 146: Effects of Low Barometric Pressure 146: Medical  
 Treatment of Anoxia 146: Acute Oxygen Want 146: Chronic Oxygen Want  
 146: Low Barometric Pressure 146: Aspiration 147, Effects of Carbon  
 Monoxide 146, Cyanide 146: Inert Gas Asphyxiation 147: Other Cases of  
 H<sub>2</sub>S, Methion, etc. 146: Summary 146: Effect of Electric Shock 146

## CHAPTER XVIII

## DISEASES DUE TO CHEMICALS AND DRUGS

147

- Introduction 146: Ethyl Alcohol 146: Acute Alcoholism 146: Chronic Alcoholism 146: Alcoholic Trance or Automatism 146, Delirium Tremens 146: Acute  
 Alcohol Hallucinations 146: White Brain 146: Korsakoff's Syndrome or Erubism  
 147: Organic Neuritis 146: Digoxin 146: Methyl Alcohol 146: Ginger  
 Turbidity 146: Opium 146: Cocaine 146: Cannabis Indica 146: Barbiturates  
 146: Lead 146: Mercury 146: Acute Arsenic Poisoning 146: Chronic Mercury  
 Poisoning 146: Arsenic 146: Ethylamine or Ethylamine 146: Ethyl 146: Ethyl  
 146: Food Infection 146: Food Intoxication (Botulism and Allantoin) 146  
 Snake Bites 146







FIG	PAGE
308 Diagrammatic cross section of the spinal cord of a pellagrin - - -	792
310 Illustrations of a case of aerodysma showing the typical distribution of the rash on the face, hands, and feet and a common position assumed by the child - - -	794
483 Foot and mouth disease in man - - - - -	1344
484 Foot and mouth disease in man showing character and distribution of lesions on the hands - - - - -	1344
486 Acute exacerbation of the original local lesion in rat bite fever - - - - -	1348
517 A case of lead poisoning showing the blue line on the margin of the gums - - -	1488
516 Slit lamp beam showing a rose brown reflex from the lens - - -	1494
51 The gray reflex of the lens on oblique illumination - - - - -	1494

# THE PRACTICE OF MEDICINE

## CHAPTER I

### AN INTRODUCTION TO THE PRACTICE OF MEDICINE

The practice of medicine is probably the most entrancing profession in the world. As it deals with human beings it requires a complete understanding of, and sympathy with, all aspects of human life. One, to practice it wholeheartedly, must be a confessor, a judge, a counselor and above all, a friend. The time of the 'family doctor' is held by some to have passed away. It would be unfortunate if such were the case. The physician who 'knew the case' from birth had a perspective to which no one else might possibly attain. The spirit of specialization and mass production has invaded the medical profession. It has probably improved and stimulated the technique and zeal of the average medical practitioner. It has undoubtedly elevated the average health of the citizens at large, but has it done so without the loss of a certain *finesse* and understanding of the human frailties and the helpful counsels of an old and trusted friend which made a profession instead of a trade of medicine? I believe that many of the rising generation of medical practitioners are returning to this humanistic relationship.

The complete understanding of the patient who seeks help is the first requisite for successful treatment. An individual seldom consults a physician unless there be something which interferes with his well being either in regard to his work or his pleasure. Thus it is so much easier to comprehend his discomfiture if one has an idea of his social and industrial environment. If one has not it is incumbent that as far as possible this should be ascertained and so from this point may a start be made. This is the present concept of the industrialist and the industrial physician.

But, in acute diseases an early diagnosis is essential. Thus it is important to have a thorough conception of the early manifestations of the acute diseases or in other words an understanding of the causation of symptoms and their importance in relation to the time interval of their occurrence. Many symptoms and signs have an entirely different significance depending upon whether their onset be acute or explosive on the one hand, or insidious or intermittent on the other. A sudden disturbance of the normal processes of the animal organism gives rise to much more violent consequences than does a gradual dislocation. The reason for this is to be found in that uncanny faculty of the animal organism which if given a sufficient period of time can marshal to its aid many compensatory means to accommodate itself to the new environment. In order therefore to recognize the processes which are being initiated it is of importance that the earliest manifestations of disease processes should

be recognized and interpreted in their proper perspective and laid to the door of a definite etiological cause which is present in all diseases if we had sufficient knowledge to recognize it

There are several ways to view diseases depending upon whether one is most interested in the living or the dead. All diseases when taken as a whole run through a reasonably definite "life cycle," although this statement must be modified to the extent that one cannot expect every instance of the same disease to run on a time schedule as to the appearance of each phase, or that each phase will be equally prominent and distinctive in each case. The fallacy of considering all diseases from the "morbid anatomical" viewpoint is that this is usually a final stage and does not sufficiently illumine the conditions of disturbed anatomy and physiology that have gone before. It is true that a great deal may be inferred from the final dissection but this in many instances does not give the clue to the variegated and important disabilities which have been present during life. Furthermore, there are numerous disturbing functional derangements which cannot be explained on any known anatomical basis. In fact death frequently occurs and no adequate anatomical explanation can be found. It, therefore, behooves all physicians, no matter what their therapeutic inclination may be to view the human organism as a going concern, subject to various functional defects or disorders, the causes of which should be understood during life. The anatomical changes found after death are of significance only if they can shed light on the cause and progress of the functional failure of the living organism.

One of the great handicaps to the practice of medicine is the isolated view point obtained of the various phases of the majority of chronic diseases. The acute diseases are usually viewed in their entirety by one physician, that is during the full period of their relatively short course. But then there is the residue or sequela which may not be manifested for years to come. The complete physician should have this opportunity but unfortunately the medical practice of the day has tended to divide into compartments. These may be only sufficiently large as to include diseases of one organ or system even individual diseases or even at times isolated symptoms. The broad panorama of disease may thus become obscured. As already mentioned diseases run through a life history which follows an immutable course barring accidents the question of time and age and rate of progress. By this is meant that chronic diseases may develop in their natural course either slowly or rapidly depending upon individual characteristics. If it be rapidly then the whole life history may be run within a short span and the chances of other disasters interrupting its course by premature exit are less likely. On the contrary the progress may be so slow as to be almost imperceptible. Then the chances of some other accident interfering with the full development of the disease are more likely.

One of the disadvantages of studying or viewing disease from the purely anatomical standpoint is the tendency to explain all disabilities solely on an anatomical basis. This is wrong except so far as when it be possible to interpret functional deficiencies as resting upon such a basis. A man without one

leg is obviously handicapped. So also is an organ without an adequate blood supply. But it is essential that we be able to determine the anatomical defect without seeing it. Therefore we must be able to reason from functional derangements that such and such anatomically progressive lesions are in the process of development. Many instances of this comprehensive functional anatomical method of deduction will be illustrated in the following pages.

When a patient seeks medical advice he brings a history of what has gone before with a definite time relationship indicating progress. He presents a certain physiological or anatomical disturbance, the magnitude of which from the point of view of the functional disturbance at the moment indicates the present stage of progress of the disease. Many of these disturbances may be of temporary significance due to unusual strain or indiscretion which by correction may recast the actual condition into its proper perspective. So a hasty judgment as to the future is inadvisable. Furthermore, a comparatively mild or unimportant malady may be exaggerated in its manifestations by an overanxious or distressed spiritual outlook or desire to entice sympathy and attention. All such factors must be carefully weighed and assessed by the discerning physician. He must view the whole progress of the disease with sympathetic understanding and keen insight into its character and that of its host.

A mere diagnosis as to the probable and fairly obvious status of the moment is not sufficient. He must be patient and capable enough to assay the present real situation and at the same time to clear the clouds of apprehension and fear, to be truthful in the presence of impending catastrophe when necessary but tempering the decision with mercy as a brave and fearless spirit oftentimes surmounts what seem impossible obstacles continuing onward in usefulness and with joy to others. It therefore behooves all physicians to beware of the absolutely hopeless prognosis with the inclination to hold out a gloomy future, futility and dependence or condemn to a short period of life. This should be avoided for two reasons: in the first place we do not always know whereof we speak and second such a statement in any case can do no good and is apt to discourage utterly one who otherwise might finish out his life in comparative cheerfulness and pleasure. It is not death that is so fearsome but the contemplation of the march toward it when the journey is known to be short. The spirit is filled with terror lest it fail.

## THE APPROACH TO THE PATIENT

An individual seeks advice of a physician either because something interferes with self preservation, self propagation or self comfort. Other things do not matter from a physical point of view. It is true they may be economic or spiritual and as such are camouflaged under a more indefinite physical disguise. But, in spite of these clouds of darkness they must be disentangled.

Probably there is no more important approach to the elucidation of 'disease' than a careful history. It is often neglected as being of little moment as compared to the 'physical findings' or the 'laboratory findings' which are presumed by many to be of greater importance. This at times is true

by pericardial effusion and scarring respectively. Soon after this Lower's fellow countryman Mayow in 1674 published his *Tractatus Quinque* in which the oxygenation of the blood in the lungs is clearly presented, Mayow's fifth treatise was one of the very earliest on rachitis\*.

Mention should be made next of two other important medical writers of the last half of the seventeenth century who although not dealing specifically with heart disease contributed significantly to the subject. Kerckring in Amsterdam in 1670 wrote a treatise on pathology called *Spicilegium Anatomicum* in which with apologies to his teachers and colleagues he pointed out their grave error in considering as evidence of heart disease the postmortem clots found in the heart by this one brief statement he altered radically the current misconception about the heart wiping out doubtless fully one half of all so-called heart disease. The other writer who did so much at that time to elucidate somewhat the still very dark subject of heart disease was Bonetus who in two editions of his *Sepulchretum* (1679 and 1700) presented among more than two thousand other case reports with clinical notes and autopsy findings several hundred whose symptoms and signs were to be ascribed to lesions of the heart and great vessels. These cases he collected from all possible sources they make an invaluable compilation which served as a basis for his successors including Morgagni one hundred years later (*De Sedibus et Causis Morborum* 1761). In this rich clinicopathologic collection there were many firsts involving all parts of the body. There were the earliest associations of dyspnea with cardiac enlargement, sudden death with calcareous aortic stenosis and collapse and early exitus with a high degree of coronary artery narrowing.

Early in the eighteenth century two important books on the heart and some of its diseases were published in France and Italy respectively by leading authorities of their day. The first entitled *Traité Nouveau du Coeur* appeared in 1715 prepared by Vieussens who in his youth thirty years before had published a pioneer work on the nervous system called *Neurographia*. An excellent description of the mechanical effect of severe mitral stenosis on the lungs with resultant congestion and dyspnea appears in this work by Vieussens. The other writer was Lancisi, physician to Pope Clement XI to whom he dedicated the volume entitled *De Motu Cordis et Aneurysmatibus* which was published posthumously in 1728. Lancisi described engorgement of the neck veins associated with dilatation of the right ventricle and discussed cardiac enlargement at some length. An illustration of the very rich nerve supply of the heart is included in this volume and was bettered only years later when in 1772 Neubauer published a drawing of a beautiful dissection of the sympathetic innervation of the heart. Lancisi was an able and prolific writer and had earlier published several books on medicine and other subjects such as fungi. One of these medical books is unique in that it was entitled *De Subi*

\* Since writing this I have within the last few months acquired a still earlier work by Mayow a fascinating booklet published in 1671 and entitled *Tractatus Duo Quorum prior agit de Respiratione Alter de Rachide*. The first printing of this little book appeared in 1668.

*taneis Mortibus (On Sudden Death)* (1707) it contained autopsy reports of individuals who had died suddenly and whose postmortem examinations had been carried out at the express request of the Pope an instance long forgotten of the liberal enlightened and scientific attitude of the Church

Now we come at last to what is often called the first textbook on heart disease itself namely the *Traite du Coeur* by Senac published in Paris in 1749. It has much more of clinical and practical importance than had been presented by any earlier publications. This is particularly true of treatment of which there was scarcely any before two hundred years ago. Senac mentions the value of bleeding and sedation in heart failure and of quinine in rebellious palpitation a very early forerunner of the relatively recent application of quinidine to the treatment of cardiac arrhythmia. Following Senac various textbooks on heart disease have appeared in different languages most of them however after a delay of a half century or more. Included among them are in French those of Corvisart Napoleon's physician (1806) Huchard (1889) Vaquez (1921) and Laubry the present leader of the French school (1930) in German those of Kreysig (1815) Traube (1856) Fraentzel (1889) Romberg (1906) Edens (1931) and Hochrein (1941) in English those of Hope (1832) Stokes (1854) Flint (1859) Steell (1906) Mackenzie (1908 4th edition 1925) Hirschfelder (1910) White (1931 the present edition the 4th 1951) and Levine (1936 4th edition 1951) in Italian those of Testa (1810) and Luisada (1938) and in Spanish that of Cossio (1935 4th edition 1949).

More important as a rule than these textbooks however have been monographs on important new techniques or on etiologic diagnostic or therapeutic discoveries beginning with Auenbrugger's introduction of percussion in 1761 in a little book in Latin entitled *Inventum Novum ex Percussione Thoracis Humani* but not well known until Corvisart's translation in 1808. Percussion was further developed by Piorry (1828) and Skoda (1839). This was the first of the techniques which have been slowly but steadily introduced into the practice of medicine to improve the diagnosis of heart disease. One of Corvisart's pupils was Laennec whose introduction in 1819 of the stethoscope for mediate auscultation of the heart and lungs was a very significant advance (*De l'Auscultation Mediate*). A century later Cabot and others began to try by electrical methods to broadcast by separate earphones or loud speaker to groups and classes the heart sounds and murmurs of an individual patient and to record them on phonographic records while simultaneously Lewis and others began to photograph on moving film by way of microphone and galvanometer the auscultatory findings with simultaneous electrocardiogram (phonocardiography). These techniques slowly evolved to their present higher degree of usefulness with the help of Einthoven and Geluk of Geckeler of Mannheim and of Sprague and Rappaport.

One hundred years ago (1846) Hutchinson introduced the determination of the vital capacity of the lungs. Another interval elapsed before the fourth helpful technic in the study of the circulation came to pass this was the



sphygmograph which first developed by Murey in 1860 gradually evolved into a practical instrument the ink polygraph in the hands of Mackenzie who printed many of his graphic records in his classic on *The Pulse* in 1902 and who with the help of Wenckebach called attention to the serious significance of pulsus alternans. The next important technic namely the sphygmomanometer was slowly introduced by a group of workers (von Basch 1881 Potain 1889 and Riva Rocci 1891) another decade or two passed before blood pressure measurement became a routine clinical procedure nearly two hundred years after the English parson Stephen Hales had accurately measured the arterial pressure of a mare in 1733.

Roentgen late in 1895 announced the discovery of his x rays and the following spring Williams of Boston published an x ray picture of the heart. In this field there has been a steady advance ever since with the introduction of orthodiagraphy of the heart by Moritz in 1902 of teleroentgenography by Kohler in 1905 of roentgenkymography by Stumpff in 1931 (suggested by Sabit in 1913) with further development recently (1945) by Chamberlain Henny and Boone by application of photoelectric cell and galvanometric graphic recording of angiocardiology by contrast injections by Forssmann in 1931 Castellanos in 1937 and by Robb and Steinberg in 1938 and of roentgencinematography by Reynolds in 1934.

Another technic of the greatest value has been electrocardiography. The study of the electrical activity of the heart introduced nearly a hundred years ago by Kolliker and Muller (1855) was carried on laboriously in the physiologic laboratories for nearly fifty years before a practical instrument (the string galvanometer) was developed by Einthoven in 1903 to replace the clumsy capillary electrometer which had been employed by Waller in 1887 to take the first human electrocardiogram. Nearly another ten years passed before clinical electrocardiography began under the stimulus of Kraus and Nicolai in Berlin and of Lewis in London. In the last twenty five years there has been a considerable amplification of the use of the electrocardiograph in the diagnosis of heart muscle injury and especially by the application of unipolar leads to the chest wall itself.

Finally with regard to special diagnostic technics one should mention cardiac catheterization which first introduced by Forssmann who experimented on himself in 1929 has now evolved through the help of Courmand Dexter McMichael Lenegre and their colleagues into a routine practical method of intracardiac and pulmonary artery blood gas and blood pressure measurements to aid in the more accurate diagnosis of congenital and other obscure cardiac defects.

Leaving the history of the introduction of the diagnostic technics which began with Auenbrugger's discovery of the value of percussion in 1761 let us proceed with other historic advances in our knowledge about heart disease and first about symptoms. In 1768 Heberden described angina pectoris and gave it its name although he did not connect it with the heart he knew that it was a dangerous symptom and that it was particularly likely to attack

middle aged males its connection with coronary artery disease was discovered by Jenner about 1772 but not published by him until 1799 in a letter to Parry which appeared in the latter's book entitled *Syncope Anginosa*. Over one hundred years went by for some obscure reason before the common coronary complication of acute thrombosis with myocardial infarction received adequate recognition as a clinical entity by Herrick in 1912 and still another decade passed before Herrick's notable contribution became widely known. Finally we owe much to Anitschkow for his demonstration of atherosclerosis in 1912 to Leary for his painstaking delineation of the lesions of coronary atherosclerosis (1935) and to Schlesinger and Blumgart for their valuable exposition of the evolution of the lifesaving coronary collateral circulation (1937-1941).

Although dyspnea had been associated for the first time with heart disease by Bonetus in 1679 having been considered a symptom solely of pulmonary or pleural disease before that time it was not until Vieussens described the mechanism of dyspnea in mitral stenosis in 1715 and Hope that of breathlessness in myocardial failure a century later (1832) that the pathogenesis began to be understood. Senac and Hope in their noted textbooks in 1749 and 1832 called attention to the fact that asthma may be a complication of a failing heart with pulmonary vascular congestion. Only in recent years as a matter of fact has there been a renewed interest in this relationship. Still another type of disturbed breathing consisting of periodic apnea and dyspnea and associated with cardiovascular disease was described by Cheyne in 1818 and Stokes in 1854\*.

Other symptoms than angina pectoris, dyspnea and palpitation that can be credited to the heart are few but there is one that has been well described namely syncope due to heart block and attended by a very slow pulse. This goes by the three names of its chief observers Morgagni (1761), Adams (1827), Stokes (1854) syndrome.

Many signs have been named after physicians but frequently not by any means after those who discovered them first or even described them best. Thus there is frequently an erroneous significance to such a designation where priority has been wrongly assigned. Where possible not only for this reason but for others too especially that of preference for a descriptive term over a proper name it is more reasonable to drop the eponym and in the future not to add such to medical literature. Examples of both the reasons noted above are water hammer instead of Corrigan pulse and chronic constrictive pericarditis instead of Pick's disease. The water hammer pulse had been well known and described long before Corrigan and Chevers had well described chronic constrictive pericarditis fifty years before Pick. There are exceptions however in which the descriptive term is so long and complicated

My attention has been called by Dr. Arlie V. Bock to the fact that Hippocrates probably referred to Cheyne-Stokes respiration in describing the case of a man who died of a fever in an extremely delirious state. This patient had unusual breathing. It was referred to as follows: "The breathing throughout as though he were recollecting to do it was rare and large" (Hippocrates, Loeb Classical Library, G. P. Putnam, New York, 1923, Vol. 1, p. 187).

or the eponym so firmly established that the observer's name may wisely be retained

As to abnormalities of pulse form and rhythm descriptions were quite completely presented by Galen in the second century A.D. and by his followers for the next 1500 years but it took many centuries before the explanation for the abnormalities was given. The water hammer pulse was attributed to free aortic regurgitation not only by Corrigan in 1832 but also by his predecessors and contemporaries. The first to ascribe the plateau or more importantly the anacrotic pulse to aortic stenosis is not clearly known as yet. The paradoxical pulse was described by Kussmaul in 1873 and attributed when marked quite rightly to pericardial disease. Extrasystoles were known to the ancients but the first reassurance about them was given by Williams in 1835 and confirmed by Mackenzie in 1902. In 1887 Bristowe described paroxysmal tachycardia as a particular entity corroborated the next year by Bouveret after whom it has sometimes been called. Auricular fibrillation was identified as a clinical condition independently by Rothberger and Winterberg and by Lewis in 1909 while auricular flutter was accurately described and named by Ritchie in 1911.

After the introduction of auscultation by Laennec abnormalities of the heart sounds and heart and blood vessel murmurs began to be described and explained. C. J. B. Williams described and explained the mitral diastolic murmur in 1835. The aortic diastolic murmur and both aortic and mitral systolic murmurs had been widely recognized before this in fact by Laennec himself. In 1862 Austin Flint described his famous murmur of relative mitral stenosis without mitral cusp deformity. In 1879 Roger reported the finding of his loud (grade 4 to 5) systolic murmur with palpable thrill just to the left of the sternum maximal in the third and fourth intercostal spaces in cases of congenital ventricular septal defect sometimes called Roger's disease. The continuous murmur of a patent ductus arteriosus was described and explained by Fagge in 1873. In 1881 Graham Steel described the pulmonary diastolic murmur of high pressure in the pulmonary artery due to mitral stenosis as a rule and named for Steel. Duroziez' name is attached to the to and fro murmur heard over a large artery during pressure by a stethoscope in cases of free aortic regurgitation (1861). Gallop rhythm and its clinical importance were pointed out by Potain in 1875.

Signs of heart failure have been recognized for many years and it was evident when the very first large collection of autopsies was made by Bonetus in 1679 that cardiac enlargement both hypertrophy and dilatation were important findings sometimes attended by dyspnea and indicative of strain although often unidentified as to type. Lancisi described in 1728 fullness and pulsation of the neck veins associated with right atrial and ventricular dilatation but many years in fact nearly two centuries went by before Mackenzie spread widely abroad this important sign of heart failure. When mediate auscultation came into common use a hundred years ago rales in the lungs especially at the bases became recognized as an evidence of pulmonary edema.

due frequently to heart failure but this sign has often been misjudged since so many other causes may be responsible Dropsy that is dependent edema and liver enlargement were described by Bonetus in 1679 and recognized early as signs of heart disease and failure as well as being due to other diseases Munro published a treatise on dropsy in 1755

Pericarditis was one of the very first cardiovascular abnormalities noted and described as seen in Benivenio's collection of autopsies in 1507 doubtless it was known to the ancients even though they did not recognize heart disease as such Galen is said to have treated surgically an infected wound under the sternum which may have involved the pericardium Effusions were well known to the compilers of postmortem data in the sixteenth and seventeenth centuries Lower described cardiac tamponade in 1669 and Ruolan (1653) followed later by Senac too advised pericardial paracentesis which was not done however so far as records go until 1819 (Romero in Barcelona) Chronic pericardial scarring was an early discovery and the first description of the special type called chronic constrictive pericarditis was apparently given by Lower in 1669 but it was not presented as a clinical entity until 1842 when Chevers of Guy's Hospital in London described it Wilks again referred to it in 1870 and finally in 1896 it was called Pick's disease after Pick who described mediastinopericarditic pseudocirrhosis of the liver Various minor signs have been attached to pericardial disease Broadbent (1895) and Ewart (1896)—see Chapter 27 Surgery for chronic constrictive pericarditis was proposed by Delorme in 1898 but not carried out until 1913 (Sauerbruch) To date hundreds of cases have now been relieved by surgery

The recognition of the types of heart disease has been of the greatest importance of all advances in the entire field of heart disease as pointed out by Cabot's classical paper The Four Common Types of Heart Disease in the *Journal of the American Medical Association* in 1914 By the early 1920's the present day fundamental classification of cardiac diagnosis based primarily on etiology had been independently introduced and well established at the Massachusetts General Hospital in Boston and at the Bellevue Hospital in New York City The major importance of this step was indicated not only by better diagnosis prognosis and treatment but especially by directing attention to the causes of heart disease the elucidation of which will doubtless lead to effective preventive medicine so much more important in the final analysis than research interesting though it is in abnormal physiology and in therapy both medical and surgical

Congenital heart disease described in scattered reports by earlier workers was first more adequately treated as such by Farre in 1814 and by Gintrac in 1824 Peacock's book on the subject in 1858 is much better known Since then progressive advances have been made in the works of Rokitsansky (1875) Abbott (1908) Laubry and Pezzi (1921) and Taussig (1947) In 1938 the present era of spectacular cardiac surgery began with the first successful closure of a patent ductus arteriosus by Gross and Hubbard al-

though Munro (1907) and others had suggested it and unsuccessful efforts had already taken place. Since then other dramatic advances in surgical therapy have been made in congenital heart disease by Blalock and Taussig (1945) and by Potts (1946) in the alleviation of the tetralogy of Fallot by Crafoord (1945) and by Gross (1945) independently in the cure of coarctation of the aorta and by Gross (1945) in breaking a ring of the great vessels around trachea and esophagus. All these advances, dramatic and vital as they are, pale however in comparison with the discovery by Gregg (1941) and Swan (1943) of Australia that congenital cardiovascular defects and cataracts are likely to be found at birth in babies born of mothers who had German measles (rubella) during the first two or three months of pregnancy.

Rheumatic heart disease as an entity was first suggested by Pitcairn (1788) and Baillie (1793) although valvular defects had been well described pathologically since the days of Bonetus (1679) and earlier. Bouillaud in 1840 established on a firmer footing the association between rheumatic fever and heart disease. Aschoff discovered his more or less specific lesion in the myocardium in 1904 and in 1913 Poynton and Paine called attention to the importance of the hemolytic streptococcus as an exciting factor confirmed by Coburn in 1931 and by others since.

Subacute bacterial endocarditis was slowly separated from other heart troubles toward the end of the nineteenth century (Osler 1885) its causative agent the *Streptococcus viridans* was discovered by Schottmüller in 1910 and the disease was much studied by Libman (1910 and later) but it remained well nigh totally fatal until Loewe showed in 1944 that the majority of the cases can be cured by penicillin.

Cardiovascular syphilis was probably the first etiologic type recognized. Aortic aneurysms were attributed to syphilis by Pare about 1564 and aortic regurgitation with the cor bovinum was recognized as sometimes of syphilitic origin a hundred or more years ago. Reuter recognized aortitis as a syphilitic lesion in 1906. Intensive antisyphilitic treatment for aortitis has been developed effectively during the present generation especially by Moore and his associates at first with the heavy metals (1932) and recently with penicillin. The most important advance however has been in preventive medicine through the early recognition and specific treatment of the chancre itself or by its prevention in the first place resulting in an impressive drop now in progress in the development of aortic syphilis fifteen or twenty years after the original infection.

Other infections bacterial and virus and parasitic infestations of the heart and blood vessels involve relatively few individuals nowadays in contrast to their frequency often unrecognized as such in days gone by before the control of these diseases became so impressive. Diphtheria, tuberculosis, influenza and other virus diseases, trichiniasis and trypanosomiasis (Chagas 1909-1922) have all been recognized and described by many workers often lost in history but they are now of minor import. One might add however

that the first actual proof of the influenza heart did not come until 1945 (Finland et al) in severe degree it is uncommon

Thyroid disease as it involves the heart is now no longer a problem but thirty years ago thyrotoxicosis was recognized as an important though not common cause of heart disease. It was attacked successfully by surgery (sub total thyroidectomy) by Lahey and Hamilton in 1923. The introduction of speedy surgical correction of thyrotoxicosis itself and of medical measures with iodine thiouracil and irradiated iodine has practically wiped out the thyrotoxic heart. The heart in myxedema was first clearly described in 1918 by Zondek it too is now very rare the disease itself having been brought largely under control.

The enlarged hypertensive heart was first described as an accompaniment of nephritis by Bright himself in 1836. In 1872 Gull and Sutton called attention to the arteriolar fibrosis found with these enlarged hearts. Both they and Bright considered that there must be present in these cases some special factor of strain although hypertension had not yet been discovered. At the end of the nineteenth century blood pressure measurements in man began and soon afterward hypertension was identified. It was considered as an entity separated from Bright's disease and called hyperpiesia by Allbutt in 1895. The hypertensive heart had been serious when of high degree and not amenable to curative therapy until the advent of lumbodorsal sympathectomy (Smithwick 1940) which has aided a large number of cases demonstrating finally that every single type of heart disease may be reversible (White 1944). The rice and low sodium diets have also helped some cases but something better than any of these measures is needed to control the hypertension various drugs are now being hopefully investigated in this direction especially the purified veratrum alkaloids in particular protoveratrine.

The cor pulmonale (or pulmonary heart disease) has only very slowly come up for recognition. The chronic type has been known for several decades (associated particularly with silicosis now under better control) but the acute cor pulmonale has only recently been described (McGinn and White 1934).

The final of the more common or important types of heart disease that due to coronary atherosclerosis has already been referred to above in the writings of Heberden, Jenner and Herriek. It remains one of the chief problems of world health today and has until the very present been much neglected in research as to etiology and pathogenesis. Interesting clues have been recently uncovered however and the future looks brighter.

Other causes of heart disease have been recognized for generations but only lately has their incidence been more clearly analyzed. Cardiac and pericardial neoplasms have been noted on pathologic examination for centuries although at first there was great confusion in the diagnosis of the simple postmortem clots which before Kerckring (1670) were called polyp and thought to indicate disease. In late years it has been possible even to make correct ante-

mortem diagnoses of neoplasm involving the heart and pericardium in a few cases. Traumatic lesions of the heart were also recognized very early but even today in nonfatal cases they comprise one of the most difficult though fortunately uncommon aspects of heart disease. Nutritional diseases involving the heart have become well recognized during the past generation especially beriberi the acceptance of which has come slowly through the work of many different individuals. Somewhat similarly has been the elucidation of other rare cardiac involvement such as is discussed in Chapter 23 of this book including conditions like sarcoidosis amyloid disease hemochromatosis and lupus.

Finally a few words may be added about other therapy than that mentioned above concerning specific types of heart disease that is in particular the treatment of myocardial and of coronary insufficiency and that of the arrhythmias. The two most important measures of treatment of myocardial and coronary insufficiency concern two medicines which have an interesting history. *Digitalis* was the Latin word coined by Fuchs from the German *Fingerhut* when he introduced that plant (the foxglove) as an afterthought in his appendix to his great herbal in 1542. From that time on for nearly two and one half centuries digitalis was officially used when it was given at all as an emetic but in a family recipe for the dropsy it held an effective though obscure place, doubtless handed down for unnumbered years until William Withering of Birmingham England in 1775 happened to be enough interested in both the practice of medicine and botany to discover through a patient of his its value in heart failure. For ten years he tested it before he published his small but justly renowned monograph on the foxglove in 1785 giving credit to Fuchs for its original introduction to medical botany. More than another century elapsed however before Withering's explicit and correct advice about dosage became current practice. During that century efforts were made to purify the crude drug and one hundred years ago Natuelle (1847) in France made digitoxin (digitaline Natuelle) which has very lately become popular in the U.S.A. Many preparations of digitalis are now available and effective meanwhile the dried leaves themselves remain a cheap and useful medicine too. In recent years there has been a tendency to give more of the drug both in distribution and in quantity than needed in contrast to its neglect for well over a century after Withering.

The second notable medicine is nitroglycerine (glyceryl trinitrate) invaluable in the treatment of periodic and frequently recurring coronary insufficiency in the form of angina pectoris. Preceded for a few years by amyl nitrite (Brunton 1867) it was introduced by Murrell in 1879 to take the place of the much less effective and less practical employment of spirituous liquor originally suggested by Heberden himself in 1768. There is today no better measure. The most important advance in its use in recent years has been its employment prophylactically, making more comfortable and safer the undertaking of certain necessary or unavoidable strains.

In the control of arrhythmias quinidine has already been mentioned. It was introduced by Frey in 1918 to control atrial fibrillation four years after

a patient of Wenckebach had rediscovered the helpfulness of quinine referred to a century and a half earlier by Senac (1749). The other most important therapy of arrhythmia has been that of the effect of epinephrine parenterally in the control of Adams Stokes attacks (Hardoy and Houssay 1917 Phear and Parkinson 1922).

Many other drugs have of course been used in the treatment of heart disease from time immemorial but brief mention may be added here simply of two. Mercury was employed centuries ago not only in the therapy of syphilis but also as a diuretic and like bloodletting for almost any disease in fact one poor girl with active rheumatic fever seriously ill at the Massachusetts General Hospital in 1846 was made miserable by the large doses of mercurial and many other drugs the use of which was the custom of the day. However it was not until Saxl in Vienna in 1920 accidentally discovered the more favorable effect of mercury given parenterally rather than by mouth that this currently important diuretic has come into its own. The other medicine which may be mentioned as an alleviator of misery though not a cure of heart disease is salicylic acid and its salts originally obtained from the bark of the swamp willow near the site where rheumatism itself was supposed to have been engendered. The salicylates have been used for generations to assuage the pains of acute rheumatic fever and as a matter of fact of other diseases such as rheumatoid arthritis for this purpose it has an essentially specific effect though the myocardial and endocardial manifestations of rheumatic fever are not appreciably helped. And now on the horizon there are appearing the important hormones ACTH and cortisone which give promise of controlling these diseases which involve the joints heart valves and connective tissues.

In closing this chapter a comment may be added about the history of diet as it applies to heart disease. In general apparently for centuries advice has been given to individuals with cardiac symptoms and signs to eat lightly and of simple foods. Mackenzie for example in his volume on *Heart Disease* published in 1908 advised small meals of whatever easily digested foods the patient himself preferred. The two important advances that have come have both been rather recent. First the addition of vitamins as needed especially when there is malnutrition often resulting from chronic heart failure on which occasion vitamin B complex and other vitamins (though not specifically vitamin E) have been helpfully added during the last generation. The much more significant advance however has been the belated recognition of the importance of a low sodium intake in the presence or under the threat of congestive heart failure with accumulation of fluid in lungs liver extremities or elsewhere in the body. A proper application of the helpful effect of a low sodium intake in the diet has been one of the great advances during the last decade. However the beginning of this dates back doubtless even before Karell in 1866 advised a very restricted milk diet consisting of only 800 cc of skimmed milk a day. Almost certainly the chief value of this diet lay in the restricted sodium rather than in the restricted fluid intake. In 1903 Widai and Lemerre were the first clearly to show that it was the salt itself that was im-



portant Allen in 1920 had used a low salt diet for hypertension and some of his cases with congestive failure were particularly benefited. It has however been Barker in 1932, Schroeder in 1941 and Schemm in 1942 who presented convincing data of the effect of decreased intake of sodium in congestive heart failure. One other diet may be mentioned because of its wide spread use in the treatment of hypertension and that is the rice diet of Kempner (1944). This diet low in protein and fat as well as in sodium has helped some patients with hypertension. The mechanism of its action has not been clarified. It is still under investigation.

In this chapter I have attempted briefly to present the trends of advance in our knowledge of cardiovascular disease but we still have more to learn in our campaign to reduce the incidence of heart disease by preventive measures than we have already learned during all the ages that have gone before.

### AN OUTLINE OF THE EVOLUTION OF OUR KNOWLEDGE OF THE HEART AND ITS DISEASES<sup>1</sup>

(Important contemporary events are to be found at  
the right side of the page in bold face type.)

#### B C

Imhotep (Egypt) 2980 B C and successors Observation of the pulse  
Hippocrates (Greece), 460 B C Treatises containing description and prognostic significance of symptoms and signs, including dyspnea and dropsy  
Aristotle (Greece) 384 B C Pulsation of the chick embryo's heart  
Erasistratus }  
Herophilus } (Alexandria) 310 B C Anatomy of the human heart

#### A D

Celsus (Rome) earliest years of first century A D *De Re Medicina* including recommendation of venesection for severe dyspnea  
Dioscorides (Greek working in Rome) *De Medicinali Materia* including the diuretic squill 60 A D

\*\* Galen (Greek working in Rome) 131 Detailed study of the pulse

**Hotel Dieu Paris, 651**  
**The Crusades**  
**Medical School at Salerno 1000**  
**St. Bartholomew's Hospital, 1123**  
**Bologna University 1156**  
**Montpelier University 1180**  
**Oxford University 1201**  
**The Inquisition thirteenth century**  
**Magna Carta 1215**  
**Cambridge University 1223**  
**Sorbonne University 1257**  
**Al Mansur Hospital at Cairo 1283**

<sup>1</sup> A single asterisk indicates important entries and double asterisks the more important entries in the historical table.

Ibn Nafis (Egypt) Pulmonary circulation 1300

The Renaissance fourteenth and fifteenth centuries

The Black Death 1348

Invention of Printing 1440

Leonardo da Vinci (Italy), 1452 Drawings of the heart

Constantinople captured by the Turks 1453

Martin Luther 1483-1546

Discovery of America 1492

Benedetti (Italy) Case of malposition of the heart 1493

#### HEART DISEASE NOT YET RECOGNIZED

1500

\* \* Benivenio (Italy) *De Abditis Nonnullis ac Mirandis Morborum et Sanationum Causis* some of the earliest autopsy proof of the existence of heart disease including cases of endocarditis and fibrinous pericarditis 1507

Berengario da Carpi (Italy) Commentary on the anatomy of Mondino (1516) with mention of a dilated heart 1521

Botallo (Italian working in France) 1530 Description of the ductus arteriosus (Botalli)

Canano (Italy) Valves in veins 1540

Mexico City Hospital 1524

\* \* Vesalius (Belgian working in Italy) *De Fabrica Humani Corporis* 1543 with description of human heart Also antemortem recognition of aortic aneurysm 1555 confirmed at autopsy two years later

\* Servetus (Spaniard working in France and Italy) Mention of the pulmonary circulation in his religious tract *Restitutio Christianismi* 1553

\* Colombo (Italy) Description of the pulmonary circulation in *De Re Anatomica* 1559

\* Fernel } (France) Aortic aneurysm ascribed to { *Medicina* 1554  
\* Pare } syphilis { *Surgery* 1564

\* Caesalpino (Italy) Introduction of term circulation with reference to movement of blood in arteries and veins, 1559

Schenck (Germany) *Observationum Medicarum Rarum* 1584 Important compilation of case records based on symptoms

1600

Fabrizio d Acquapendente (Italy) *De Venarum Ostiis (Venous Valves)* 1603 Creation of the anatomical theater at Padua

Albertini (Italy) *De Affectionibus Cordis* 1618 The first extensive treatise on the heart but with little important information largely a review of ancient and medieval theories with long discussion of palpitation and syncope

The Thirty Years War, 1618-1648

Aselli (Italy) Discovery of lacteal vessels 1622

- \*\* Harvey (Englishman studying in Italy) *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus* 1628 Proof of the circulation of the blood

The Commonwealth (Cromwell) in England 1649-1660

Pecquet (France) Description of the receptaculum chyli and thoracic duct 1651

Bartholin (Denmark) Discovery of lymph vessels 1653

Malpighi (Italy) *De Pulmonibus* containing a note on the discovery of capillaries 1661

Plague in London 1666

Great fire of London 1666

- \*\* Lower (England) *Tractatus de corde* 1669 This includes the experimental proof that dropsy may result from venous obstruction
- \*\* Kerckring (Holland) *Spicilegium anatomicum* 1670 Recognition that postmortem clots in the heart are not polyps or worms their faulty interpretation had caused confusion for centuries
- \* Mayow (England) *Tractatus duo* 1668 and *Tractatus quinque* 1674 Demonstration of the function of breathing to change venous blood to arterial blood by interchange of gases the blood taking up the nitro-aerial spirit of the air in the lungs
- \* Stensen (Denmark) First description of the tetralogy of Fallot 1672
- \*\* Bonet (France) *Sepulchretum* 1679 Storehouse of case reports with autopsies containing many instances of cardiovascular disease such as that of the Parisian tailor who dropped dead in the street and showed post mortem a calcified stenosed aortic valve

Siege of Vienna 1683

Peter the Great (Russia) 1689-1725

1700

Cowper (England) Plate showing aortic stenosis 1705

Floyer (England) *Physician's Pulse Watch* 1707 Recommendation of the recording of the pulse rate in health and disease

- \*\* Vieussens (France) *Traite du cœur* 1715 Description of coronary circulation Thebesian vessels (Thebesius 1716) and a few abnormalities of the heart including mitral stenosis and dyspnea therefrom

Albertini Hippolito (Italy) Cardiac palpation as an aid to diagnosis 1726

\*\* Lancisi (Italy) *De Motu Cordis et Aneurysmatibus* 1728 Discussion of cardiac and aortic enlargement and description of engorgement of neck veins with dilatation and failure of the right ventricle Also *De Subitaneis Mortibus* 1707 The first treatise on sudden death with autopsy findings in five cases

\* Hales (England) *Hæmaticks* 1733 First study of blood pressure

\*\* Senac (France) *Traite du cœur* 1749 Important textbook on the heart including observations on congenital defects and the use of quinine for rebellious palpitation

Munro (England) *Treatise on dropsy* 1755

\*\* Morgagni (Italy) *De Sedibus et Causis Morborum* 1761 Extensive discussion of pathology with many cardiovascular observations including calcification of the coronary arteries

\*\* Auenbrugger (Austria) *Inventum Novum* 1761 Introduction of mediate percussion in the study of heart size and of pericardial and pleural effusions

\*\* Heberden (England) *Angina pectoris* 1768

\*\* Neubauer (Germany) *Cardiac nerves* 1772

Lavoisier (France) *Respiratory gas exchange* 1777

Sandfort (Holland) *Early description of tetralogy of Fallot* 1777

U.S.A., 1783

\*\* Withering (England) *An Account of the Foxglove* 1785 Introduction of digitalis in the treatment of dropsy

\* Parry (England) *Thyrotoxicosis and its effect on the heart* 1786

Pitcairn (England) *Rheumatism of the heart* 1788

French Revolution 1789

Baillie (Scotland) *Morbid Anatomy* 1793 Description of endocarditis

\*\* Jenner (England) The relationship of angina pectoris to coronary disease presented in a letter published by Parry in his *Syncope Anginosa* 1799

1800

Scarpa (Italy) *Arteriosclerosis* 1804 He also gave an excellent description of the nerves of the heart in his *Tabulæ Neurologicæ* in 1794

\* Corvisart (France) *Maladies du Cœur* 1806 Important textbook on the heart He also restored Auenbrugger's percussion as an important method of examination 1808

Burns (Scotland) *Angina pectoris due to myocardial ischemia* Textbook on diseases of the heart 1809

Wells (U.S.A.) *Cardiac rheumatism* 1810

\* Testa (Italy) *Malattie del cuore* 1810

- Farre (England) Cardiac malformations including the tetralogy of Fallot 1814
- \* Hodgson (England) *Treatise on the Diseases of Arteries and Veins* 1815
- Kreysig (Germany) Textbook on heart diseases 1815
- \* Cheyne (Ireland) First good description of Cheyne Stokes breathing 1818
- \*\* Laennec (France) *De l'Auscultation Mediate* 1819 Introduction of the stethoscope
- Romero (Spain) Pericardial paracentesis 1819
- Guinrac (France) *Maladie bleue (morbus caeruleus)*, 1824
- \* Adams (Ireland) Classic description of the Adams Stokes syndrome 1827
- Hodgkin (England) Aortic insufficiency 1827
- Andral (France) Pulmonary arteriosclerosis 1829
- \* Hope (England) *A Treatise on Diseases of the Heart and Great Vessels* 1832 containing a description of left ventricular failure with pulmonary vascular congestion and cardiac asthma
- \* Corrigan (Ireland) Aortic insufficiency, 1832 The Corrigan pulse
- Lobstein (France) Arteriosclerosis 1833
- Williams C J B (England) *The Pathology and Diagnosis of Diseases of the Chest* 3rd edition 1835 Description of the mitral diastolic murmur, among other murmurs
- Bouillaud (France) *New Researches on Acute Articular Rheumatism* (with its relationship to acute and chronic endocarditis and pericarditis) 1836
- \*\* Bright (England) Association of heart disease with kidney disease 1836
- Magnus (Germany) Respiratory function of the blood 1837
- \* Skoda (Austria) Treatise on percussion and auscultation 1839
- \* Purkinje (Bohemia) End branches of the atrioventricular bundle—the Purkinje fibers 1839 He also described the visual toxic effects of digitalis
- \* Chevers (England) Description of chronic constrictive pericarditis 1842
- \* Hall (England) Sudden death due to arrest of coronary circulation 1842
- \* Weber Brothers (Germany) Vagal inhibition of the heart 1845
- Nativelle (France) Introduction of digitoxin (digitaline) 1845
- \* Hutchinson (England) Introduction of the determination of the vital capacity of the lungs 1846
- \* Ludwig (Germany) Introduction of the graphic method 1847

## 1850

- Bernard (France) Vasomotor nerves 1851
- Stannius (Germany) Heart block 1852
- Kirkcs (England) Peripheral embolism from valvular vegetations 1852
- \* Stokes (Ireland) Textbook on heart disease 1854

- \* Kölliker and Müller (Germany) Cardiac electricity 1855
- \* Vierordt (Germany) Sphygmography introduced 1855
- Virchow (Germany) Thrombosis and embolism 1856
- Peacock (England) *Malformations of the Heart* 1858
- Foster (England) Rhythmicity of the heart 1859
- Marcey (France) Sphygmograph 1860
- Duroziez (France) Vascular murmurs of free aortic regurgitation 1861
- Flint (U S A ) The murmur of relative mitral stenosis 1862
- \* Raynaud (France) Vasoconstriction in the hands 1862
- Karell (Russia) Restricted diet in heart failure 1866
- \* Kussmaul (Germany) Periarthritis nodosa 1866 Pulsus paradoxus 1873
- Brunton (England) Amyl nitrite introduced for angina pectoris 1867
- \* Fick (Germany) Blood flow studies 1870
- \* Da Costa (U S A ) Irritable heart of soldiers 1871
- \* Traube (Germany) Description of alternation of the pulse and of cardio-renal disease 1872
- \*\* Gull and Sutton (England) Arterio-capillary fibrosis 1872
- Welch F H (England) Differentiation of aortic syphilis from aortic atheroma 1875
- Rokitansky (Austria) Septal defects 1875
- Southey (England) Tubes for anasarca 1877
- Welch W H (U S A studying in Germany) Acute pulmonary edema 1878
- \*\* Sanderson and Page (England) Study of heart action by capillary electrometer 1878
- Rosenbach (Germany) Cardiac reserve 1878
- Roger (France) Murmur of interventricular septal defect 1879
- \* Murrell (England) Nitroglycerine introduced in treatment of angina pectoris 1879
- Winiwarter (Germany) Endarteritis 1879
- Barie (France) Traumatic lesions of the heart valves 1880
- \* von Basch (Germany) Introduction of the sphygmomanometer 1881
- Gaskell (England) Heart block 1881
- Steell (England) Murmur of functional pulmonary regurgitation 1881
- Concato (Italy) Polyserositis 1881
- Leyden (Germany) Coronary artery disease 1884
- Osler (Canada U S A and England) Bacterial endocarditis 1885
- \* Waller (England) Human electrocardiography 1887
- \* Bristowe (England) Paroxysms of tachycardia 1887
- Fallot (France) Congenital heart disease—Fallot's tetralogy 1888
- \* Bouveret (France) Paroxysmal tachycardia 1889
- \* Riva Rocci (Italy) Development of sphygmomanometer 1891
- Kent (England) } Atrioventricular bundle 1893
- His (Germany) }
- Bayliss and Starling (England) Electrocardiographic studies 1893

- \* **Einthoven and Geluk** (Holland) Phonocardiography 1894
- Allbutt (England) Hyperpiesia 1895
- Broadbent (England) Pericarditis 1895
- Ewart (England) Signs of pericardial effusion 1896
- Porter (U S A ) Coronary circulation 1896
- \* **Marie** (France) Myocardial infarction 1896
- Farina (Italy) and Rehn (Germany) Operations on the heart 1896
- Pick (Germany) Chronic mediastinopericarditic pseudocirrhosis of the liver 1896 Chronic constrictive pericarditis first described by Chevers in 1842
- \* **Williams** (U S A ) Roentgen ray study of the heart 1896 Roentgen introduced the new ray in 1895
- \* **Delorme** (France) Pericardial resection suggested 1898
- Gibson (Scotland) Textbook on heart disease 1898
- Fiedler (Germany) Interstitial myocarditis 1899

## 1900

- \*\* **Mackenzie** (Scotsman working in England) *The Study of the Pulse* 1902
- \* **Moritz** (Germany) Orthodiagraphy of the heart 1902
- Brauer (Germany) Precordial rib resection 1902
- Carrel (Frenchman working in U S A ) Arterial suture 1902
- Matas (U S A ) Aneurysmorrhaphy 1902
- \*\* **Einthoven** (Holland) Introduction of the string galvanometer for electrocardiography 1903
- \* **Wenckebach** (Hollander working in Germany and Austria) Arrhythmia of the heart 1903
- \* **Widal and Lemerre** (France) Low sodium intake for congestion 1903
- \*\* **Aschoff** (Germany) Myocardial lesions in rheumatic fever 1904
- Pal (Austria) Vascular crises 1905
- \* **Kohler** (Germany) Teleroentgenography 1905
- \* **Korotkow** (Russia) Auscultatory sphygmomanometry 1905
- Romberg (Germany) Textbook on heart disease 1906
- Reuter (Germany) Demonstration of *spirochaeta pallidum* in aorta in syphilitic aortitis 1906
- Keith and Flack (England) Discovery of the sinoatrial node 1907
- Tawara (Japanese working in Germany) The atrioventricular node and its connection with the bundle its branches and the network of Purkinje fibers 1908
- Buerger (U S A ) Thromboangitis obliterans 1908
- Abbott (Canada) Congenital defects 1908
- Trendelenburg (Germany) Pulmonary embolectomy 1908
- Pachon (France) Oscillometry, 1909
- \* **Rothberger and Winterberg** (Austria) Atrial fibrillation recognized clinically 1909

## EVOLUTION OF OUR KNOWLEDGE OF THE HEART 21

- \* Lewis (Welshman working in England) Atrial fibrillation recognized clinically independent observation 1909 Blood vessels of the skin 1927
- Schottmuller (Germany) Identification of the *Streptococcus viridans* as the cause of subacute bacterial endocarditis 1910
- \* Lian (France) Left and right sided heart failure 1910
- Hirschfelder (U S A ) Textbook on heart disease 1910
- Libman (U S A ) Subacute bacterial endocarditis 1910
- \* Ritchie (Scotland) Atrial flutter 1911
- \*\* Herrick (U S A ) Clinical recognition of coronary thrombosis 1912
- Anitschkow (Russia) Atherosclerosis 1912
- Krogh and Lindhard (Denmark) Blood flow 1912
- Sauerbruch (Germany) Pericardial resection 1913
- \*\* Cabot (U S A ) Etiology of heart disease 1914

### World War I, 1914-1918

- Cohn (U S A ) Digitalis effect on T wave of the electrocardiogram 1915
- Eggleston (U S A ) Digitalis dosage 1915
- Jonnesco (Roumania) Sympathectomy for angina pectoris 1916
- \* Oppenheimer, et al (U S A ) Neurocirculatory asthenia 1918
- \* Smith (U S A ) Coronary electrocardiogram 1918
- Levine and Tranter (U S A ) Myocardial infarction 1918
- \* Frey (Germany) Introduction of quinidine in the treatment of atrial fibrillation 1918
- Zondek (Germany) The heart in myxedema 1918
- Christman (U S A ) Digitalis in normal rhythm 1919
- Pratt (U S A ) Digitalis strength 1919
- Wyckoff (U S A ) Classification of cardiac diagnosis 1919

### Specialization

- \* Pardee (U S A ) Coronary T waves of the electrocardiogram 1920
- \*\* Saxl (Austria) Mercurial diuretic injections 1920
- Rehn (Germany) Pericardial resection 1920
- Reid (U S A ) Effect of arteriovenous fistula on heart 1920
- Gross (Canada) Coronary artery injections 1921
- Vaquez (France) Textbook on heart disease 1921
- \* White and Myers (U S A ) Classification of cardiac diagnosis 1921
- Krogh (Denmark) Capillary physiology 1922
- Key (Sweden) Embolectomy 1922
- Chagas (Brazil) Cardiac trypanosomiasis 1922 (1909)
- Scott (U S A ) Quinidine for ventricular paroxysmal tachycardia 1922
- Plummer (U S A ) Iodine in the initial treatment of thyrotoxicosis 1923
- Hering (Germany) Carotid sinus reflex 1923



- \* Hamilton and Lahey (USA) Cure of thyrocardiacs by subtotal thyroidectomy (the first clear demonstration of the reversibility of heart disease) 1924
- Schmieden (Germany) Pericardial resection 1924
- Cutler (USA) Valvulotomy 1924
- Parkinson (England) Epinephrine in Adams Stokes attacks 1924
- Rowntree and Adson (USA) Bilateral lumbar sympathectomy for hypertension 1925
- Mandl (Austria) Paravertebral nerve injection for angina pectoris 1925
- Cannon (USA) Accessory cardiac nerves Discovery of sympathin from the thoracic sympathetic chain 1926
- Blumgart and Weiss (USA) Velocity of blood flow 1927
- Wenckebach and Aalsmeer (Holland) Beriberi heart 1928
- \* Kleefer and Resnick (USA) Angina pectoris 1928
- Keith et al (USA) Malignant hypertension 1928
- Weber (Czechoslovakia) Electrocardiogram in familial periodic paralysis associated with potassium lack, 1928
- Erdheim (Austria) Medionecrosis aortae idiopathica 1929
- von Gierke (Germany) Glycogenic visceral enlargement 1929
- \* Forssmann (Germany) Cardiac catheterization 1929 angiocardiography 1931
- Edens (Germany) Textbook on heart disease 1929
- Churchill (USA) Pericardial resection 1929
- Laubry (France) Textbook on heart disease 1930
- \* Wilson (USA) Bundle branch block 1930 Direct and chest leads in electrocardiography 1930-1936
- Grant (Scotsman working in England) Arteriovenous anastomoses 1930
- Coburn (USA) Hemolytic streptococcus infection and rheumatic fever 1931
- \* Wood and Wollerth (USA) Precordial leads in coronary occlusion 1932
- Manca (Italy) Virus myocarditis (mumps) 1932
- Blumgart Levine and Berlin (USA) Total thyroidectomy for angina pectoris and heart failure 1933
- Goldblatt (USA) Hypertension produced by renal ischemia 1934
- Shennan (England) Dissecting aortic aneurysms 1934
- Leary (USA) Coronary atherosclerosis 1935
- Beck (USA) Pericardial implantation of pectoral muscle to bring new blood vessels to the heart seriously affected by coronary disease 1935
- \* McGinn and White (USA) Acute cor pulmonale 1935
- \* Castellanos (Cuba) Angiocardiography in disease 1937 Robb and Steinberg (USA) 1938
- \*\* Schlesinger and Blumgart (USA) Coronary occlusions and collateral circulation 1937-1941

Winkler Hoff and Smith (U S A ) Electrocardiograms in potassium poisoning (including uremia) 1938 1941 Chamberlain et al 1939 Keith et al 1942

Taussig (U S A ) Tricuspid atresia 1938

\* Gross and Hubbard (U S A ) Successful ligation of patent ductus arteriosus 1939

\* Smithwick (U S A ) Radical splanchnic resection for hypertension 1940 (Development of Peet's operation 1935 )

Mannheimer (Switzerland) Calibrated phonocardiography 1939

#### World War II 1939-1945

Link et al (U S A ) Dicumarol as anticoagulant 1940

Hahn (U S A ) Blood volume determined by radioactive iron 1940

\* Gregg Swan (Australia) Congenital defects due to rubella in pregnancy 1941-1943

Hubbard (U S A ) Excessive tachycardia in young infants as a cause of marked cardiac enlargement 1941

Rappaport and Sprague (U S A ) Phonocardiography 1941-1942

Cournand Richards et al (U S A ) Cardiac catheterization and determination of right heart blood pressure 1941 1944 McMichael (England) 1944

Kempner (U S A ) Rice diet for hypertension 1944

Aub et al (U S A ) Bacterial toxic factor in shock 1944

Elkin (U S A ) Arteriovenous fistulae and their surgical correction 1944

Chavez (Mexico) National Institute of Cardiology Mexico 1944

\* Loewe (U S A ) Cure of subacute bacterial endocarditis by penicillin 1944

\* White (U S A ) Reversibility of heart disease 1944

Henny Boone and Chamberlain (U S A ) Elektokymography 1945

Finland et al (U S A ) Influenzal virus myocarditis 1945

Blakemore Lord and Whipple (U S A ) Portal hypertension and portal venal shunts for relief thereof 1945

\* Blalock and Taussig (U S A ) Operation for tetralogy of Fallot 1945 (Potts 1946)

\* Crafoord (Sweden) Operation for coarctation of aorta 1945

\* Gross (U S A ) Operation for coarctation of aorta 1945 surgical relief for tracheal obstruction from a vascular ring 1945

Lenegre (France) } Intracardiac electrocardiograms 1946

Hecht (U S A ) }

Dexter (U S A ) Determination of pulmonary blood pressure 1946

Taussig (U S A ) Congenital heart disease 1947

#### National Heart Institute U S P H S., 1948

Blumgart et al (U S A ) Radioactive iodine therapy of refractory coronary and myocardial insufficiency 1948

- Bland and Sweet (U S A ) Venous shunt for mitral stenosis, 1948  
 Brock (England) Surgery for pulmonary stenosis 1948  
 Murray (Canada) Repair of ventricular and atrial septal defects 1948  
 Kraye (U S A ) Protoporphyrin in hypertension 1949  
 Hench et al (U S A ) ACTH in rheumatism 1949  
 Bailey } U S A Operations on mitral valve for stenosis thereof 1949-1950  
 Harken }

## BIBLIOGRAPHY

- Bonetus T *Sepulchretum* Leonard Chouet Geneva 1679 2nd ed (Mangetus)  
 Cramer and Perachon Geneva 1700  
 "Cardiology as a Specialty" Editorial *Lancet* 1947 I 873  
 Corvisart J N *Essai sur les Maladies et les Lésions organiques du Cœur et les gros Vaisseaux* Migneret Paris 1806  
 Garrison F H *An Introduction to the History of Medicine* W B Saunders Co Philadelphia 4th ed 1929  
 Herrick J B *A Short History of Cardiology* Charles C Thomas Springfield Ill 1947  
 Hope J A *Treatise on the Diseases of the Heart and Great Vessels* William Kidd London 1832  
 Lancisi J M *De Motu Cordis et Aneurysmatibus* J M Salvioni Rome 1728  
 Osler W *The Evolution of Modern Medicine* Yale University Press New Haven 1923  
 Senac J B *Traité de la structure du cœur de son action et de ses maladies* Briasson Paris 1749  
 Vieussens R *Traité Nouveau de la Structure et des Causes du Mouvement naturel du Cœur* Jean Guillemette Toulouse 1715  
 White P D "The Reversibility of Heart Disease" *Illinois M J* 1944 LXXXVI 9  
 Cardiology as a Specialty *Am Heart J* 1947 XXIII 161

---

PART I

CARDIOVASCULAR EXAMINATION  
SYMPTOMS and SIGNS

---



---

## CHAPTER 2

---

### THE RANGE OF THE NORMAL HEART

Six years have elapsed since this chapter was written as a useful introduction to this volume few changes in it have been necessary since in this interval of time little has been added to our knowledge of the range of the normal heart despite the great interest and importance of the subject occasioned by the examination of many hundreds of thousands of healthy young men for military service

---

It is requisite that every intelligent Patient should try his Pulse in a Morning in his Health that he may inform his Physician what number of Pulses he has in a perfect Health by which a Physician may judge of his natural Constitution and the Physician may know how far the diseased Pulse exceeds from the natural Numbers and whether the Numbers of the Pulse are increased or be deficient by which he may discern whether tis a hot or a cold disease so wrote Sir John Floyer in 1707 in the *Pulse Watch*

The words I have just quoted make up one of the rare examples in medical literature old or new not only of the recognition of the wide range of bodily measurements and functions of humankind in health but what is still more important also of a relatively simple and accurate method of determining changes denoting abnormality in any given individual thus avoiding the many clumsy and inaccurate measures that have been devised for general use

The range of the normal heart remains today in cardiovascular physiology one of the most difficult problems accurately to assess and in the diagnosis of cardiovascular disease one of the most important and yet neglected subjects It is astonishing to find relatively so little written about it in works on medicine by either ancient or modern authors As a matter of fact the ancients actually paid more attention to the problem than have the moderns largely without doubt because they had to do so since they didn't even recognize the existence of heart disease Galen Avicenna and other authorities of the classical and medieval ages tried for example in their analysis of the pulse which is as far as they got in cardiology to explain all variations on the basis of age sex temperaments (hot cold moist and dry) seasons of the year climate locality food and drink sleep and waking athletic exercise

pregnancy pain disease elsewhere in the body and emotional states (anger delight, joy grief and fear) Under the circumstances they did an extraordinarily good job in showing how all of these conditions may affect the pulse many of us today might profitably take a leaf from their book

In the sixteenth century the pendulum began to swing back a little when autopsies revealed through the findings of chronic heart lesions the fact that the heart could be diseased and yet life continue Gradually as more and more evidence of the frequency and multiplicity of heart disease was discovered the impetus of the backswing of the pendulum accelerated through the centuries until it reached its maximum (we hope) early in the nineteenth century with such authorities as Corvisart Napoleon's physician He asserted that heart disease was with the single exception of pulmonary tuberculosis one hundred times the most common of all organic diseases in France both in public and in private practice He thought the majority of cases of asthma hydrothorax and various other conditions were the result of heart disease and that cardiac fatalities were very likely more numerous than deaths due to lesions of brain stomach liver kidneys and other organs combined He even scorned the idea of the need of statistical proof for these remarks He attributed the frequency of heart disease to the hard or rather constant work of the heart and to the passions of mankind

Just thirty years later however in 1836 John C Williams of Edinburgh wrote a book on *Practical Observations on Nervous and Sympathetic Palpitation of the Heart Particularly as Distinguished from Palpitation the Result of Organic Disease* (Figure 1) He deplored the frequency with which functional derangement of the heart was attributed to heart disease itself and brought the pendulum a wee bit back from the extreme swing the reverse of Galen's for which Corvisart and others of that day and since were responsible He wrote that *palpitation* was

frequently by a careless observer regarded as symptomatic of some serious organic or structural change being established either in the coverings of the heart its muscular texture or in some of its valvular appurtenances A careful and deliberate inquiry however he went on to say 'will in the generality of cases enable us to strip them of their apparent obscurity and danger and reduce them to their true place in nosological arrangement' Latterly there has been too great a rage for tracing diseases almost exclusively to vascular derangement I deprecate this because I am convinced of the unceasing influence of the nervous system both in health and in disease A deservedly popular writer on medicine of the present day says 'The longer we live the more we see and the deeper we study so much the more shall we become convinced that not only are the primary impressions of morbid causes sustained by the sentient system of the human fabric but it is here the primary morbid movements first begin and are thence propagated to the vascular apparatus which from that moment reacts upon and is again influenced by the nervous system No man I am satisfied can ever be a sound Pathologist or a judicious practitioner who devotes his attention to one of these systems in preference or to the exclusion of the other through life they are perpetually acting and inseparably linked together

PRACTICAL OBSERVATIONS  
ON  
NERVOUS AND SYMPATHETIC  
PALPITATION OF THE HEART,  
PARTICULARLY AS DISTINGUISHED FROM  
PALPITATION  
THE RESULT OF ORGANIC DISEASE  
TO WHICH ARE PREFIXED SOME GENERAL REMARKS ON THE  
USE OF THE STETHOSCOPE  
AND  
EMPLOYMENT OF PERCUSSION  
IN DIAGNOSIS OF DISEASES OF  
THE HEART AND LUNGS  
BY JOHN CALTHROP WILLIAMS, M D

EDINBURGH

PHYSICIAN TO THE NOTTINGHAM DISPENSARY AND TO THE NOTTINGHAM  
UNION HOSPITAL AND DISPENSARY LECTURER ON THE PRINCIPLES  
AND PRACTICE OF PHYSIC EXTRAORDINARY MEMBER OF THE  
ROYAL MEDICAL SOCIETY EDINBURGH  
&c

---

Quo quis recti cogitatio debet, et sanitas  
Candidus impetrit, si quid est, et  
satis nunciat, nec in — Hon

---

LONDON  
LONGMAN, REES ORME BROWNE AND CO PATERNOSTER ROW  
NOTTINGHAM J HICKLIN JOURNAL OFFICE  
1836

FIG 1 Title page of book by John C Williams 1836 on nervous and sympathetic palpitation of the heart



Williams also quoted the late eminent Dr. Baillie as follows:

"There are in truth few phenomena which puzzle, perplex and lead into error the inexperienced (and sometimes the experienced) practitioner so much as the inordinate action of the heart. He sees or thinks he sees some terrible cause for this tumult in the central organ of the circulation and frames his portentous diagnosis and prognosis accordingly. In the pride of his penetration he renders miserable for the time the friends—and by his dreadful countenance damps the spirits of his patient. But ultimate recovery not seldom disappoints his fears and the Physician is mortified at his own success."

Finally Williams presented several case reports, the most striking of which was that described by Morgagni of a boarding mistress who had palpitation. She was bled with some appearance of relief. The palpitation returned and so she was bled again daily until she died. Nothing abnormal was found at autopsy in thorax or abdomen and Morgagni wrote:

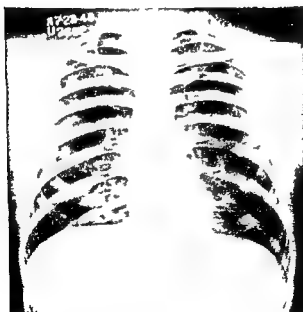
*It would have been well had her physician remembered that the very name of Palpitatio Cardiaca implies a course of proceeding quite the reverse.*

Like the rest of the body the heart varies in size and shape and action from one person to another, somewhat according to sex and age and body size. Even when we take into careful consideration these three factors, however, the range of the normal heart is too wide for us to know whether or not there has been some slight enlargement from strain or infection or otherwise, or some slight change in shape, or a change in action in almost any given case. This is true even of postmortem measurements of weight and volume and shape, and all the more so of clinical findings by physical examination or by x-ray electrocardiographic and physiologic measurements of the circulation (Figure 2). I do not mean that this difficulty should prevent us from constructing and utilizing tables based on our present knowledge, but we should clearly recognize their inadequacy and seek better correlative factors than we have at our disposition to date. Body build, aside from size, largely a family inheritance, is unquestionably of great importance and yet we have largely neglected it. Other bodily measurements besides height and weight and surface area need evaluation. We have found, for example, that the hearts of identical twins resemble each other closely on physical examination and by x-ray study and electrocardiography, although it is still possible to distinguish by minor details the electrocardiogram of one twin from that of the other.

Moreover, in a given person one must use great judgment in comparing the findings from day to day or hour to hour based on clinical examination. The height of the diaphragm is of the greatest importance, especially in the analysis of x-ray films and electrocardiograms (Figures 3, 4 and 5); it changes constantly, not only with ordinary breathing but with the amount of food or air in the stomach, the bulk of the contents, solid or gaseous, of the intestines, the enlarging uterus in pregnancy, the addition of fat which is so



A



B

FIG 2 A comparison of the appearance of the heart shadows in roentgenograms of two individuals without heart disease who died noncardiac deaths and who showed at autopsy heart weights of 200 grams each without any evidence of cardiovascular abnormalities

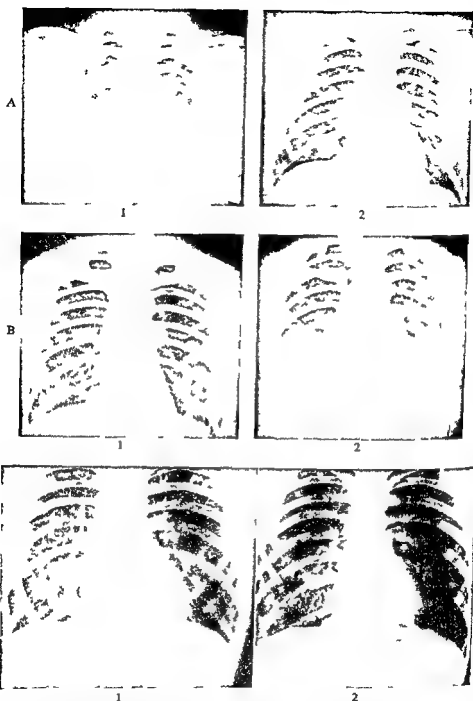
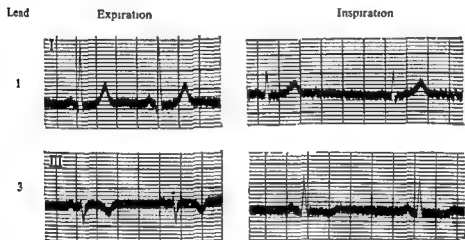


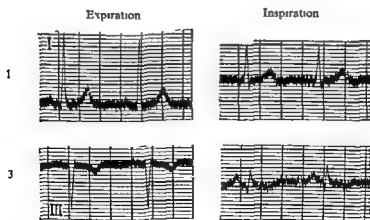
FIG 3 Roentgenograms of the thoraces of normal young men showing the effects on the heart shadows of alteration of the level of the diaphragm in respiration (A) Short stocky physician (1) during quiet breathing in upright position (2) at height of full inspiration in upright position (B) Slender young physician (1) during quiet breathing in upright position (2) at height of full expiration in upright position. Note the similarity of A1 and B2 and of A2 and B1

(C) BW male age 27 (1) Normal control deep inspiration immediate exposure T D 14.6 cm height of diaphragm 13.1 cm (2) Effect of Valsalva's experiment deep inspiration followed by forced expiration against 40 mm Hg for 5 second T D 14.2 cm height of diaphragm 12.4 cm T H = transverse diameter of heart

often deposited in the abdomen or in its wall certain intra abdominal diseases particularly resulting in enlargement of liver or spleen ovarian cyst or ascites diaphragmatic herniation and finally with certain intrathoracic diseases especially those that cause an extreme pulmonary emphysema with deep lowering and little motion of the diaphragm. It is often not realized that the prolonged fixation of the diaphragm at the level of full held inspiration (simulating the Valsalva experiment) results in an appreciable decrease in the size of the x ray heart shadow (Figure 3C) this can result in erroneous estima



A



B

FIG 4 Electrocardiograms (Leads 1 and 3) from two normal individuals (A) and (B) showing the effect of deep expiration and inspiration on the deviation of the electrical axis

tion of heart size if roentgen studies of the lungs are used for cardiac appraisal (see Chapter 7)

Besides the height of the diaphragm the position of the body itself makes a difference (Figure 6). One should always stipulate therefore whether an examination physical x ray or electrocardiographic is made in the upright position or recumbent. In our own cardiographic laboratory years ago we

Lead

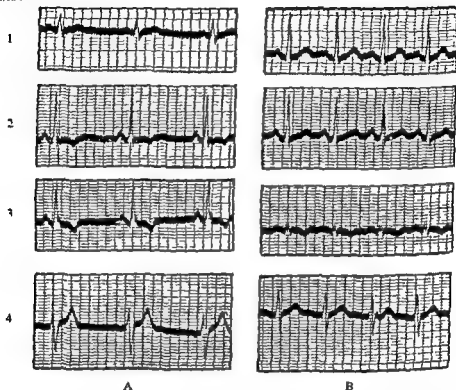


FIG 5 Electrocardiographic changes (4 leads) with respiration in normal healthy man of stocky build (A) At height of full inspiration (B) At height of full expiration. Lead 4 was taken with exploring electrode over the fifth intercostal space at the left midclavicular line and the remote electrode on the left leg (Graybiel and White *Electrocardiography in Practice* W B Saunders Company Philadelphia 1941 Figures 16 and 17)

didn't record the position although the tracings were almost always made with the patient sitting comfortably. In the last ten years however since we found what a difference position may (though it usually does not) make we have recorded by a simple straight line the angle of the patient's body. Positions of diaphragm and of body influence not only the anatomic and electric angle of the heart in the frontal plane but result in a rotation which is also important in its effects though not so easy to measure.

The immediate state of health is another vital factor frequently influencing the heart findings on examination. A heart perfectly normal to start with

and even later on showing normal myocardium endocardium valves and pericardium at autopsy may dilate acutely or subacutely from the effect of severe hypochromic anemia massive pulmonary embolism (to produce the acute cor pulmonale) and paroxysmal tachycardia at excessive rates as for example in the case of infants where the heart rate may reach 300 or more a minute and result not only in general cardiac dilatation but also in congestive failure with engorgement of the liver. Some of these infants have been erroneously diagnosed as having the so-called idiopathic hypertrophy of the heart and some have been wrongly regarded as abdominal emergency



Lead

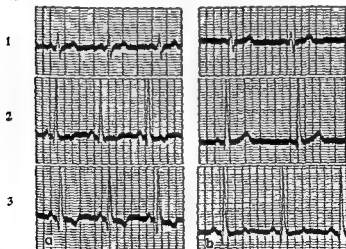


FIG 6 Roentgenograms of the thorax of a healthy young man (above) and electrocardiograms (limb leads) of another healthy young man (below) both slender in build showing the effect of change in body (and heart) position—(A and a) sitting upright (B and b) lying supine

cases for example pyloric stenosis because of the vomiting caused by the acute congestive failure. Severe infectious diseases may also alter the presumably normal cardiac findings on examination without producing actual heart disease. Acute rheumatic infection can of course precipitate acute or subacute cardiac dilatation and failure from the rheumatic myocardial disease, and diphtheria may seriously affect the myocardium but leaving these two specific infections out there are still other infections like pneumonia which may cause temporary systolic murmurs and even electrocardiographic changes especially in rapidly growing or delicate individuals. Whether these murmurs are to be ascribed always to slight dilatation or how much the speeding up of blood flow has to do with them we don't know. It is clear however that thyrotoxicosis without producing actual heart disease in the acute cases can alter the findings on examination of the heart not only in producing a tachycardia and increased pulse pressure but by the increased pulmonary blood flow causing marked accentuation of a physiologic pulmonary systolic murmur and a bulging of the pulmonary arc in the x-ray picture simulating a mitral shape of heart shadow.

How much the factor of physical strain is responsible for changes in heart size and shape in man we don't know. Once upon a time the medical profession as well as the laity talked glibly of the athletic heart. When most athletic hearts were shown to be something else the term went into the discard and now we doctors say almost as glibly that there is no such thing as an athletic heart. However a revision of the past and present opinions is still awaited on the basis of most careful studies not yet adequately assembled. There is a hint from several sources including an annual appraisal of Harvard oarsmen which was for some years conducted by various associates of mine that an occasional or more likely a rare person may after some years of excessively strenuous sport develop an increase in heart size out of keeping with any increase in body size. This sort of change is reasonable to expect in view of experimental evidence in animals where it has been shown that long-continued physical exercise produces hearts that are distinctly larger than those of animals kept very quiet and in view of the well known fact that hares have relatively very much larger hearts than have rabbits racing greyhounds than other dogs and race horses than ordinary mounts. Exercise can of course produce transient systolic murmurs mostly in the pulmonic area or increase those already present even in normal persons. Another point of interest is that a trained athlete tends to have a slow pulse or one that slows quickly after exercise although I can well remember counting the pulse rate of the winner of a marathon race a few years ago and finding it faster (118) at the starting line before he had taken a step than at the finish (110) after running 26 miles in his case nervous tension as to the outcome of the race was doubtless responsible acting like stage fright. I would hasten to add however that there is no evidence that vigorous exercise in the case of a healthy person in good training hurts the heart. If anything the reverse is true as pointed out by Morgan in a volume entitled *University Oars* published by

Macmillan in London in 1873 in this book data are presented which indicate that the Cambridge and Oxford oarsmen of a hundred years or more ago outlived their expectation. It may well be that the change to a very sedentary life is more harmful than a maintenance of exercise.

The effect of high altitude on the heart and circulation is in rare individuals an important consideration. Not many persons have exposed themselves to altitudes of 12 000 feet or more as permanent residents or even temporarily but now of course with the circulatory adjustments in aviators especially in military service the problem has become acute. Circulatory collapse probably antedates serious cardiac involvement itself in mountain climbers and in aviators in the latter either from the effect of low oxygen tension in the atmosphere or from the centrifugal force of great speed and change in direction or from still other factors. Residents at very high altitudes do however show circulatory adjustments that have been well described and resemble somewhat those in the cyanotic type of congenital heart disease at sea level. Tandler has pointed out incidentally that the bird *Lagopus* living in the Alps has a heart weight 50 per cent greater than that of the *Lagopus* of the same size living at lower altitudes.

The factor of the effect of rapid growth on cardiac findings has not yet been completely assessed. It is the impression of many of us that a fast growing boy or girl or indeed a delicate child of any age is very prone to show an instability of circulation and heart action and easily induced heart murmurs from fatigue overexertion or mild infection that do not signify the presence of heart disease or active rheumatism which we are so prone to suspect in our climate in New England and rightly so of course in many cases. We need more enlightenment in this problem.

I have already referred to pregnancy as a factor which alters the height of the diaphragm and so affects both x ray picture of the heart and electrocardiogram but it has other results too. Through the influence of the increased blood volume and circulation the heart volume is itself somewhat increased and pulmonary and even apical and aortic systolic murmurs may appear due in part to such factors and in part to the upward displacement of the heart and great vessels.

Still further factors significantly affecting the action of the normal heart are the emotions as pointed out by the ancients and restated by Williams. Not only may fear and pain alter heart rate blood pressure heart sounds and subjective sensations but through action on the sympathetic and parasympathetic nerves they may even alter the electrocardiogram. With tachycardia the T waves are often depressed and on occasion excessively so even inversion of the T waves has been induced by sudden fright as it has been also but doubtless through a different mechanism by drinking ice water.

And finally we come to the toxic influences of drugs or poisons on the normal heart. Those that are best known are the effects of digitalis atropine and quinidine but there are doubtless less well known drug actions or the influence of rare poisons that need exploration. This is an important digres-



sion for toxic effects on an otherwise normal heart may simulate serious disease as was so well borne out in the famous insurance racket in New York City some years ago when a few crooked doctors lawyers and insurance clients conspired to defraud the companies by the production of ill health and electrocardiographic changes by large amounts of digitalis these symptoms and signs being attributed to coronary disease I myself have taken experimentally, moderate to large doses of digitalis and have not only altered my electrocardiogram with lengthening of *P R* intervals and depression of *S T* segments and *T* waves and induced anorexia and nausea but also caused disagreeably forceful heart action at an ordinary rate as well as extrasystoles and paroxysms of tachycardia Atropine while producing tachycardia lowers the *T* waves of the electrocardiogram as well as does the inhalation of tobacco smoke epinephrine (adrenaline) lowers and may even invert the *T* waves in Lead 2

In later chapters I shall take up in some detail the actual measurements anatomic and physiologic that are considered to be within the range of the normal heart blood vessels, and circulation and shall also in later chapters discuss symptoms and signs that may be the result of either cardiovascular diseases or of other factors not related to such diseases There still tends to be overdiagnosis of heart disease by the erroneous application of both subjective and objective data I have spent almost as much time in correcting wrong diagnosis of heart disease based on normal variations as I have in establishing or confirming the presence of actual heart disease One of the most common of all errors is that of including a large triangle of fat at the cardiac apex as a part of the heart shadow in roentgenologic cardiac mensuration (Figure 7)

In concluding this chapter I have still another observation to make closely related to the present subject and fundamental It may well be the most important thing I shall have presented in this book It is doubtless often a subject of thought but there has been surprisingly little reference to it especially as it relates to the heart Can we tell when an organ is strictly normal? After all what is normal? The word comes from the Latin *norma* which means rule pattern or carpenter's square Normal health is supposed to be a state of the body in which disease is not discoverable May there not be a few grams of increase in heart weight from one strain or another without lack of ease or objective evidence resulting? May there not be quite extensive change in the coronary arteries of many of us even with narrowing and perhaps small or gradual symptomless occlusions here and there with no lack of ease and with perfectly normal electrocardiograms? And we may have to be run over at ninety or die of pneumonia which proves resistant to chemotherapy Are these coronary changes even if they do produce electrocardiographic abnormalities in old age to be regarded as disease or may they not be considered like gray hairs as a part of the natural process of growing old? When does natural aging stop and disease begin? I find incidentally a great help in using this conception in talking to patients who are going through an acute or chronic

process of adjustment of their coronary circulation with coronary insufficiency so often a temporary state lasting but a few weeks or months or a year or two. It is a comfort for the patient to realize that there is not actually a 100 per cent difference between his coronary arteries and those of his friend who feels perfectly well; there may be only 3 or 4 per cent. He himself may be just over the threshold of clinical evidence and his friend just under.

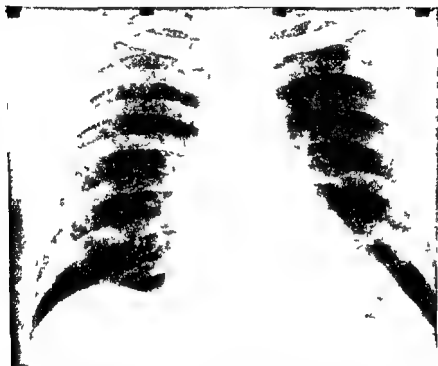


FIG 7 Roentgenogram of healthy fat man showing a large triangle of epicardial fat at the pericardiophrenic angle on the left a common source of error in estimation of heart size

In summary then let me repeat that we need much more study of normal controls than we possess at present of the heart in all types of mankind and by all methods of examination especially x ray analysis and electrocardiography. In the past we have all rushed to what has seemed more interesting and exciting namely the evidence of diseased states so that actually at the present time we are likely to be more thrilled by separating from the category of manifestations of disease certain normal findings than we are to discover disease itself. We have put the cart before the horse but it is not too late to change about. In the study of pulse rate and blood pressure range we do now have normal standards based on hundreds of thousands of individuals but there is still some uncertainty as to interpretation of borderline readings especially of those in the upper range how high for example may blood pres

sure readings, both systolic and diastolic rise in a normal person from nervousness alone? We need many thousands of normals for x ray heart measurements and electrocardiograms and at the same time better correlations with body build so that we may construct more accurate tables always avoiding however blind worship of formulas and figures. Even statistical analysis helps us but little here for there is still a chance that an individual with measurements at the outer range of normal among thousands of carefully studied cases may himself or herself be either healthy or diseased.

Hence until we acquire adequate information and even when we have it we can save ourselves a lot of worry and uncertainty as to whether any given individual has acquired an abnormality of the heart by following Floyer's advice and making a careful routine examination including x ray film and electrocardiogram while the subject is still in excellent health. A comparison of serial data on a given person is more valuable than checking him or her against any standard tables.

Finally when all is said and done the borderline between the perfectly normal and the slightly but definitely abnormal is so wide not only clinically but anatomically as well that it is unlikely that we can ever draw a sharp line between them nor should we try too hard so to do.

## BIBLIOGRAPHY

### INCLUDING GENERAL REFERENCES ON CARDIOVASCULAR DISEASE

- Clark A J *Comparative Physiology of the Heart* Cambridge University Press New York 1927
- Corvisart J N *Essai sur les Maladies et les Lésions organiques du Cœur et des gros Vaisseaux* Migneret Paris 1806
- Floyer John *The Physician's Pulse Watch* Sam Smith and Benj Walford London 1707
- Hillman C C Levy R L Stroud W H and White P D *Studies of Blood Pressure in Army Officers. Observations Based on an Analysis of the Medical Records of 27741 Officers of the United States Army* *JAMA* 1944 CXXV 699 and CXXVI 879 1945 CXXVIII 1059 and CXXIX 585 1946 CXXXI 951 1947 CXXXV 77
- Morgagni J B *De Sedibus et Causis Morborum* Typographia Remondiniana Venice 1761
- Morgan J E *University Oars* Macmillan & Co Ltd London 1873
- Smith H L *The Relation of the Weight of the Heart to the Weight of the Body and of the Weight of the Heart to Age* *Am Heart J* 1928 IV 79
- Tandler J *Anatomie des Herzens* Gustav Fischer Jena 1913
- Vierordt H *Anatomische physiologische und physikalische Daten und Tabellen zum Gebrauche für Mediziner* Gustav Fischer Jena 3rd ed 1906 (1st ed 1881)
- Wiggers C J *Modern Aspects of the Circulation in Health and Disease* Lea and Febiger Philadelphia 2nd ed revised 1923 (1st ed 1915)
- Williams John C *Practical Observations on Nervous and Sympathetic Palpitation of the Heart Particularly as Distinguished from Palpitation the Result of Organic Disease to Which are Prefixed Some General Remarks on the Use of the Stethoscope and Employment of Percussion in Diagnosis of Diseases of the Heart and Lungs* Longman Rees Orme Browne and Co London 1836

---

## CHAPTER 3

---

### THE PATIENT'S HISTORY AND SYMPTOMS

The present chapter and the next after careful scrutiny as in the case of Chapter 2 have required but minor changes. They may I hope continue to be helpful especially to those not already expert in the field of cardiology and to those more experienced who have become careless or hurried in their history taking, and physical examinations and who are still too numerous

---

#### THE PATIENT'S HISTORY

The diagnosis and treatment of heart disease are dependent upon the history and examination of the patient. The capacity to elicit the significant symptoms and signs, the ability to analyze these symptoms and signs after they have been found, the knowledge of the best therapy, and not the least important of all the quick appraisal of the sort of person to be treated are all essential to the satisfactory practice of medicine. In one's early days in medicine, in school and for a while afterward, the analysis of symptoms and signs and to a lesser extent their treatment may be learned with a fair degree of success, the ability to elicit the symptoms and signs and the understanding of the individual patient and his reactions are taught less easily by word of mouth or book but come gradually with experience. Without this experience in practice one may continue but half trained, although able to discourse learnedly on diagnosis and treatment. No amount of reading or discussion can take the place of prolonged hard work in the clinic or in the homes of patients; the science of medical practice cannot be taught in the classroom.

It is therefore impossible for me to do more in this discussion of examination and of symptoms and signs than to point the way and to trust that eventually proficiency may come to each individual who rounds out with his own experience such information as he may find in this and other books. Any physician may and doubtless will discover in time innovations or modifications of our present methods of examination and analysis whereby the study and treatment of cardiovascular disease can be furthered. Progress in the last generation has been rapid and has been advanced at a fast pace in the last twenty years since the publication of the first edition of this book. We have at hand a far better chance to diagnose and to treat heart disease successfully

than had our fathers and there is no reason why this march should not continue. With our wealth of methods of examination however there is danger that we may become overconfident or neglectful. Sometimes physicians tend to abandon old and tried methods for the new while at other times they shun new and useful methods because they fear they are but transient or because they cannot or do not want to take the time to master them or even to understand them. But often diagnosis is so difficult and signs are so misleading that we must make use of all the best tried methods at our disposal before we have properly dealt with a difficult case.

In the first part of the book which takes up the examination of patients I shall discuss briefly the methods that have proved valuable and shall have little to say about other methods of less or of doubtful value. I shall also discuss the results of these examinations that is the analysis of symptoms and signs, reserving for later parts of the book a detailed consideration of the causes, significance and treatment of the cardiovascular conditions revealed by these symptoms and signs.

First and most important of all is the story of the patient himself together with a careful consideration of his personality and reactions as he tells his own story. If told by someone else especially in the absence of the patient the story has a certain amount of value dependent on the narrator's intelligence and the closeness of his acquaintanceship with the patient but this procedure prevents insight into the case that may come only by listening to the patient's own discussion of his history and symptoms. It has been my custom in private practice to allow a full half hour and sometimes longer for the new patient's history except in very simple or special cases. I am convinced that this time has been more profitably spent than that of any other part of the examination. Not only has it revealed direct information often of great value but it has indirectly revealed knowledge of the type of person recounting his history and most important of all it has almost invariably secured the sympathetic cooperation of the patient. Detailed and careful history taking is by no means the general rule. It is to be sure, sometimes difficult or impossible in general practice but even when possible it is frequently neglected more I believe in Europe than in the United States. Its cultivation is worth serious effort and should not be left to a secretary or assistant. It is better to rely on an assistant's physical examination than on his history taking if both cannot be accomplished by oneself. I have also found it best for the trained physician to take his own notes of the history during the interview this is preferable to dictation to a secretary or assistant whose presence tends quite naturally to act as a check on free discussion.

The patient's history had best begin with a very detailed account of the present illness but under no condition should it be left at that. In some cases to be sure it may be necessary temporarily to postpone the rest of the history because of fatigue or serious illness or for another reason but it is essential to remember that significant clues or guides to diagnosis, prognosis and treatment may rest in the past history of illnesses, operations or accidents in the

opinions or treatment of other doctors (often neglected especially by hospital internes) in the social and occupational history in the account of the patient's habits and last but not least especially from the viewpoint of prognosis, in the family history another frequently neglected source of information

### SYMPTOMS

The personal story of the exact onset of the very first heart symptom should be the foundation stone on which the examination of the cardiac patient rests. One sentence accurately and adequately presenting this information may be more valuable than all the other data put together. An error or vagueness at the beginning may be seriously misleading. It is important to remember that not only may cardiac symptoms be confused with noncardiac symptoms but even when cardiac symptoms pain dyspnea and palpitation are actually present they may be confused with each other as in a case of paroxysmal tachycardia wrongly diagnosed angina pectoris or of angina pectoris wrongly labeled breathlessness because of hasty questioning. The development of the first symptom its evolution and the appearance of other symptoms must be carefully recorded according to date circumstances character intensity variability and relationship in order to gain full advantage from all available clues.

Symptoms are dependent on two primary factors (1) stimulation of sensory nerves and (2) sensitiveness of the nervous system. The percentage of responsibility of each factor must be judged in every case; it is constantly varying even in the same case at different times. Thus a relatively insensitive nervous system may give rise to no symptoms even when there is apparently considerable cause for stimulation while a sensitive nervous system may produce symptoms with very little stimulation. If fatigue lowers the threshold of the relatively insensitive nervous system symptoms may be produced by stimulation which before was ineffective; if rest raises the threshold of the sensitive nervous system symptoms may no longer be caused by the stimulation heretofore effective.

Symptoms do not mean disease; they indicate temporary disturbance of function whether or not dependent on structural pathologic changes.

I shall consider first the three most important symptoms of cardiovascular origin—pain respiratory disorders and palpitation—and after that a group of less important symptoms.

**Pain** (πόνος, penalty) of cardiovascular origin. In the first place it must be realized that pain in the chest may or may not be caused by trouble with heart or great vessels and that heart trouble may be responsible directly for pain that is outside the chest (referred pain) even when there may be no simultaneous chest pain. There are still obscurities about the transmission and interpretation of sensory nerve impulses from the heart but an increasing interest in the autonomic nervous system in the last two decades gives promise of clearing away many of the problems (White J. C. 1935). It has for example

been demonstrated in recent years that cardiac pain is carried to the central nervous system by the first four or five dorsal rami communicantes on each side by way of the corresponding ganglia from the first (stellate) down and not by way of the cervical sympathetic chains and stellate ganglia alone

Before proceeding to the kinds of heart and great vessel pain, it is important to emphasize that discomfort due to breathlessness or palpitation is not to be called pain although it is true that actual pain may accompany breathlessness or be induced by heart action responsible also for palpitation

Thoracic pain for which heart and great vessels are responsible is best discussed under seven headings (1) precordial aching or heartache, and short sharp stabs of pain (2) substernal oppression either transient (lasting a few minutes) as in the case of paroxysmal angina pectoris or of longer duration (lasting often for hours) as in the case of acute coronary occlusion (3) angina hypercyanotica (4) the pain of acute pericarditis (5) the pain of acute rheumatic carditis (6) pressure pain from aortic aneurysms and (7) the tearing pain of dissecting aneurysms of the aorta Whether pain results from the acute cor pulmonale per se is as yet problematic because of the presence of the underlying acute pulmonary embolism which may itself produce great distress in the anterior thorax or induce coronary pain in a patient who already has considerable coronary artery narrowing or cause pain from the resulting pleuropulmonary infarction An interesting and important cardiac cause of *right upper quadrant abdominal pain* is acute engorgement of the liver with stretching of its capsule secondary to abrupt failure of the right ventricle it may occur paroxysmally on effort (Boyer and White 1942) The most common or important noncardiac causes of substernal or anterior chest pain to be differentiated from the types described above are spasm of esophagus or stomach (cardiospasm) sometimes with hiatus hernia pleurisy muscle and joint discomfort neuritis herpes zoster mediastinal or other intrathoracic tumors pneumothorax and mediastinal emphysema and neurosis

1 *Precordial aching or heartache* maximal as a rule in the center of the left breast is the commonest kind of heart pain It may be very mild moderate or very severe and wax and wane for hours to years rarely does it last as short a time as a few minutes on any one occasion When severe it may radiate all over the anterior thorax and even into the arms especially down the left arm in such cases it is easily mistaken for angina pectoris Also when it is severe it is often accompanied by precordial tenderness which is a vitally important clue to the proper interpretation of the heartache itself The essential cause of this kind of pain is oversensitiveness of the nervous system from fatigue or other factor it is characteristic of the majority of cases of neurocirculatory asthenia (see Chapter 22) If it is found in the presence of heart disease itself it is to be interpreted only as a complication and not as a direct result of the heart disease it is however true that the larger the heart and the more forceful its action the more likely are heartache and precordial tenderness to be present The pathogenesis is probably that of the thumping of the heart whether normal or diseased against an oversensitive thoracic wall

*Short sharp stabs of pain in the precordium* are to be fundamentally explained in the same way as *precordial aching*, the immediate cause of such a stab as if from a pin a needle or a knife is in many cases a premature beat or extrasystole

Thus heartache and precordial stabbing sensations are unimportant and in fact often reassuring so far as serious disease is concerned the majority of patients showing such symptoms have no heart disease at all The idea once expressed that myocardial fatigue in chronic heart disease may produce these symptoms has not been borne out in the studies of the last decade or more An interesting observation concerning the *side ache* that not infrequently occurs in either left or right upper quadrant of the abdomen on exertion in normal persons has been presented by Capps (1941) he ascribes this ache to anoxia of the diaphragm on either side

2 *Substernal oppression dependent on coronary insufficiency* is also common but it is of far greater significance than heartache so far as prognosis is concerned It may be mild moderate or severe and may or may not show transmission of pain to arms neck jaws or back Many times heartache of no importance is more severe than angina pectoris of great importance The substernal oppression is almost invariably the result at first of considerable effort under special circumstances such as hurrying for a train on a cold morning in fall or winter directly after breakfast in comparison to the heart ache of neurocirculatory asthenia which occurs at any time especially when fatigue sets in at the end of the day Substernal oppression dependent on coronary insufficiency is usually at first paroxysmal lasting but a few minutes at a time as such it has been called angina pectoris (see Chapter 21) When it lasts for hours it is due most commonly to myocardial infarction resulting from acute occlusion of one of the main coronary arteries or branches in almost all cases the result of thrombosis on an atherosclerotic background but in rare cases due to embolism (see Chapter 21) Tenderness over the sternum in cases of substernal oppression does not occur unless there is a complication of neurocirculatory asthenia Actual coronary disease atherosclerotic or otherwise is fundamentally responsible for the large majority of all cases showing substernal oppression dependent on coronary insufficiency in a few cases other factors such as syphilitic aortitis anemia or possibly even coronary spasm itself are wholly or in major part responsible

Sometimes the site of angina pectoris is a little to the left of the sternum (rarely to the right of the sternum) rather than directly substernal very infrequently is it in the middle of the left breast where the more prolonged heartache described above is located and rarely does coronary insufficiency give rise only to referred pain in one or both arms hands or jaws without substernal oppression—in such cases the greatest care and judgment are necessary in its interpretation

3 *Angina hypercyanotica* is rare A heavy pain precordial and substernal with or without radiation is felt by some individuals who have considerable cyanosis especially by a few with marked mitral stenosis or massive pulmonary



embolism and is due probably to myocardial anoxia it has been called *angina hypercyanotica*

4 *Heart pain of acute pericarditis* is not common. The majority of cases of pericarditis acute or chronic have no pain but if there is involvement of certain parts of the parietal pericardium in particular that adjoining the pleura or outer diaphragmatic portion of the pericardial sac there may be disagreeable pain resembling that of pleurisy and usually aggravated by respiration (Capps 1927) the fact that the pain of pericarditis is almost always much increased by the act of inspiration is a very important clue in distinguishing it from the pain of myocardial infarction with which otherwise it may easily be confused. The pain originating in the diaphragmatic pericardium tends to be referred to the left shoulder. An acute pericardial effusion may cause a vague dull precordial oppression.

5 *Heart pain of acute rheumatic carditis* consists of precordial pain sharper than that of the heartache of neurocirculatory asthenia but not so sharp generally as the pain of acute pericarditis although it may complicate the latter. It recurs as a rule for a few days during a severe rheumatic infection in childhood. It is not a constant finding. Its pathogenesis is not clear.

6 *Aortic aneurysm pressure pain* is a severe more or less constant ache in upper thorax neck or shoulder dependent on pressure of the growing aneurysmal sac against surrounding tissues especially bones cartilage and nerves it usually requires morphine or alcohol injection of nerves (see Chapter 28)

7 *The pain of a dissecting aortic aneurysm* is usually excruciating and tearing located substernally or in the back and radiating through the chest from back to front or vice versa and often down the back to the legs. It tends to be at its height at the very outset in contrast to the pain of coronary occlusion which takes a few minutes to work up to its severest intensity. It lasts for hours and usually ends in death due to secondary rupture of the aorta into pleura pericardium, or elsewhere. It is due to the extensive tearing of the media of the aortic wall often through its entire length from aortic valve to bifurcation at the common iliac arteries and in large part circumferentially also. It is likely to be confused with the pain of acute coronary occlusion (see Chapter 28)

**Disorders of respiration** There are only three fundamental disorders of respiration that are related to heart disease itself. These are (1) dyspnea that is difficult breathing (2) cardiac asthma and (3) periodic apnea and hyperpnea or the so-called Cheyne Stokes respiration. Rapid breathing (tachypnea without dyspnea) slow breathing (bradypnea) and sighing respiration are not directly related to heart disease although they are sometimes so misinterpreted particularly the last named. Sighing is an important clue when excessive to neurocirculatory asthenia which may or may not complicate heart disease (Figure 8 and Chapter 22)

1 *Dyspnea* (i.e. difficult and noisy breathing) is of course not pathognomonic of heart disease it has many other causes chiefly pulmonary dis-

eases acute and chronic pleurisy with and without effusion bronchial asthma diseases or obstruction of the upper respiratory tract larynx and trachea mediastinal diseases diaphragmatic hernias and certain nervous affections The dyspnea produced by heart disease is mainly the result of a reflex action on the respiratory center from engorgement of the pulmonary circulation Such pulmonary vascular congestion is produced most commonly by failure of the left ventricle and less commonly by the obstruction due to mitral valve deformity (stenosis regurgitation or both) sometimes wrongly interpreted as

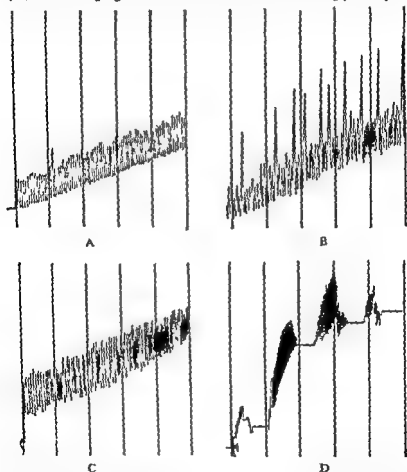


FIG 8 Spirograms showing several types of respiration (A) Normal respiration over interval of 5 minutes Inspiration shown by upstroke and expiration by downstroke Respiratory rate = 14 to 16 per minute Time interval 1 minute (B) Sighing respiration in case of neurocirculatory asthenia without heart disease Ten sighs are recorded in the interval of 5 minutes Respiratory rate = 12 to 15 (C) Dyspnea due to congestive heart failure Note increase in respiratory rate from 14 to 22 toward the end of 5 minutes at which time it was necessary for the patient to change from the supine to the erect position Note the absence of sighing respiration (D) Cheyne-Stokes respiration The durations of the three hyperpneic phases which are completely shown are 50 55 and 30 seconds respectively and of the three apneic phases 40 35 and 30 seconds respectively

the result of failure of the right ventricle. Actual effusion of edema fluid into the pulmonary alveoli in some cases undoubtedly adds its effect in exaggerating the dyspnea probably chiefly through stimulating the respiratory center by the oxygen lack and increased carbon dioxide in the blood. Failure of the right ventricle with resulting stasis and disturbed gas content of the blood supply to the respiratory center is another cause of cardiac dyspnea but less common and later in appearance. Many cases with right ventricular failure, constrictive pericarditis or tricuspid stenosis and elevated venous pressure have little or no dyspnea. It is probable that such chronic cases accommodate themselves more or less to the high venous pressure, increased blood carbon dioxide and decreased blood oxygen in contrast to the dyspneic reaction of acutely congested cases. Moreover it is of interest to observe occasionally the disappearance of dyspnea (due to left ventricular failure) when the right ventricle fails secondarily and no longer maintains the congestion of the lung vessels.

*Orthopnea* (*ορθο* erect and *πνοη* breathing) is the term applied to dyspnea sufficient in degree to force the patient to assume a sitting position. Such a position acts by gravity to relieve some of the congestion in lungs and brain.

2. *Cardiac asthma* (*ασθμα* gasping). When congestion of the pulmonary circulation occurs suddenly as the result either of acute failure of the left ventricle (see Chapter 30) or of tachycardia in cases of marked mitral stenosis (see Chapter 26) the tension or emphysema (*εμ* into and *φισσημα* a blowing sound) that ensues may by nervous reflex action precipitate asthmatic breathing. This is cardiac asthma. It is not adequately described by any other term such as paroxysmal dyspnea or acute pulmonary edema. Of course there is always dyspnea in such cases but asthmatic respiration is a particular type of dyspnea. Moreover there may or may not be clinically so-called frank pulmonary edema in these cases; that is, the blood vessels may be greatly engorged with or without interstitial edema but with no actual fluid in the alveoli and bronchioles. In fact the squeaking rales of pulmonary emphysema and asthma are much more common in these patients than are moist rales.

An attack of cardiac asthma most commonly comes suddenly at night when a patient with chronic heart disease is sound asleep with head and thorax low in position. It may infrequently occur on unusual effort when awake. The kind of heart disease is that causing severe strain on the left ventricle, especially hypertension, aortic stenosis or regurgitation or coronary thrombosis, except in rare cases of marked mitral stenosis when tachycardia due to exercise or excitement or occurring paroxysmally suddenly floods the pulmonary circulation.

It is important to note that pulmonary congestion or edema may occur acutely or chronically without asthma; that asthmatic breathing occurs often without any heart disease at all, but that in an 'asthmatic type' of individual cardiac asthma is precipitated by acute congestion of the pulmonary circulation. It is as Hope pointed out over one hundred years ago (1832), merely bronchial asthma due to bronchiolar spasm added to and set off by heart

failure (see Chapter 30) Cardiac asthma like bronchial asthma is helped though less dramatically by theophylline ethylene diamine (aminophyllin) administered intravenously

3 *Periodic apnea and hyperpnea (Cheyne Stokes respiration)* is not pathognomonic of heart disease but it occurs most frequently in chronic cardiac cases with left ventricular weakness combined with an especially poor blood supply to the respiratory center It comes on at first commonly during sleeping hours and tends to begin in very slight degree that is with waxing and waning of respiration but not actually apnea and hyperpnea it is not then such an important sign but its progress should be watched for when it is present during the waking hours it is a serious prognostic sign It is the result of alternating overstimulation of the respiratory center by blood oxygen lack and carbon dioxide excess and overdepression by blood oxygen excess and carbon dioxide decrease It is best treated by stimulation of the respiratory center by theophylline ethylene diamine (aminophyllin) or caffeine along with routine treatment of the myocardial weakness (see Chapter 30)

**Palpitation** (from the Latin *palpitare* to throb) Palpitation is a much less important heart symptom than pain and dyspnea It consists of an unpleasant sensation of the heart's action whether slow or fast regular or irregular It is usually the result of unimportant disturbance of heart rhythm namely premature beats or extrasystoles and paroxysmal tachycardia (see Chapter 32) or of forceful regular heart action rapid or slow the result of effort excitement toxic effect (for example from tobacco) or infection in a nervously sensitive person Infrequently it may be caused by a more important disorder of heart rhythm such as atrial fibrillation atrial flutter or heart block (see Chapters 33 and 34) In addition to the sensation of palpitation in the thorax there is frequently a sensation of pulse throbbing in the head or extremities more often in the arms than in the legs This is usually regular and forceful and due to effort excitement nervousness fever thyrotoxicosis or reaction to various substances ingested or inhaled for example alcoholic drinks tobacco nitrites It is not per se a sign of heart disease though it is increased in the presence of aortic regurgitation or other cause of a full pulse pressure If present in an observer it may sometimes be difficult to distinguish between his own pulse and the pulse of the subject being examined except by rate

**Other symptoms** There are several other symptoms frequently occasionally or rarely associated with heart disease but not often directly related Exhaustion nervousness insomnia dizziness headache cough hoarseness hemoptysis faintness syncope anorexia and pain in abdomen or legs are usually but incidental to various complications of heart disease examples are periodic pain in the legs on walking due to arteriosclerosis and faulty blood supply to the muscles (intermittent claudication) and nervousness due to neurocirculatory asthenia Dizziness faintness and even circulatory collapse are sometimes wrongly accredited to heart disease (for example acute coronary occlusion) when actually a severe grade of Meniere's syndrome is present with

faulty function of the internal ear the clue rests in the presence of marked *vertigo* (with nausea as a rule) which is not a symptom of heart disease although mild grades of Meniere's syndrome are frequent accompaniments of hypertension and the degenerative types of heart disease in older persons

Several noncardiac symptoms are at times directly related to heart disease. Insomnia may be the result of a poorly defined orthopnea secondary to left ventricular failure and pulmonary vascular congestion. Anorexia and upper abdominal pain may be due to engorgement of liver, stomach and intestines secondary to right ventricular failure. Syncope (with or without convulsions) may be the result of prolonged cerebral anemia secondary to ventricular standstill in heart block of high degree or to extreme tachycardia in paroxysms and rarely a manifestation of angina pectoris, a sensitive carotid sinus reflex or a vasovagal reflex of other cause. Cough dry in character and sometimes metallic or brassy in quality may result from pressure on air passages or recurrent laryngeal nerve through the presence of aortic aneurysms, very large hearts or massive pericardial effusions. Irritation of pleura or of diaphragm in acute pericarditis may also occasion cough. Both cough and hemoptysis may be due to pulmonary vascular congestion in cases of left ventricular failure and of mitral stenosis. Hoarseness may appear in rare cases of aortic aneurysms and mitral stenosis. Dysphagia may be caused by a saccular or dissecting aortic aneurysm, anomalous aortic arch, dilated left atrium or a large pericardial effusion.

## BIBLIOGRAPHY

### THE PATIENT'S HISTORY SYMPTOMS

SEE ALSO GENERAL REFERENCES FOLLOWING CHAPTER 2

- Adams R. Cases of Diseases of the Heart Accompanied with Pathological Observations. *Dublin Hosp Rep* 1827 IV 353
- Bloomfield A. L. Dysphagia with Disorders of Heart and Great Vessels. *A J M Sc* 1940 CC 289
- Boyer N. H. and White P. D. Right Upper Quadrant Pain on Effort. An Early Symptom of Failure of the Right Ventricle. *New England J Med* 1941 CCXXVI 217
- Capps J. A. Pericardial Pain. An Experimental and Clinical Study. *Arch Int Med* 1927 XL 715
- Capps J. A. and Coleman G. H. *An Experimental and Clinical Study of Pain in the Pleura, Pericardium and Peritoneum*. Macmillan Co. New York 1932
- Capps R. B. "Cause of So-Called Side Ache that Occurs in Normal Persons. Personal Observations. *Arch Int Med* 1941 LXVIII 94
- Cheyne J. "A Case of Apoplexy in which the Fleishy Part of the Heart was Converted into Fat. *Dublin Hosp Rep* 1818 II 216
- Currens J. H. and White P. D. "Cough as a Symptom of Cardiovascular Disease. *Ann Int Med* 1949 XXV 528
- Hamman L. Spontaneous Mediastinal Emphysema of the Lungs. *Tr A Am Physicians* 1937 LII 311 and *Bull Johns Hopkins Hosp* 1939 LXIV 1
- Harrison T. R., Calhoun J. A., Cullen G. E., Wilkins W. E. and Pilcher C. Studies in Congestive Heart Failure. XV. Reflex versus Chemical Factors in the Production of Rapid Breathing. *J Clin Investigation* 1942 XI 133

- Hope J *A Treatise on the Diseases of the Heart and Great Vessels* William Kidd  
London 1832 ■ 205
- Kellogg F and White P D "The Clinical Significance of Precordial Tenderness—  
The Relationship of Such Tenderness to Pain" *New England J Med* 1932 CCVI  
659
- Lewis T *Pain* Macmillan Co New York 1942
- McGinn S and White P D "A Follow up Report on the Clinical Study of Two  
Hundred and Fifty Cases of Cardiac Asthma and a Survey of an Additional Group  
of Twenty two New Cases" *New England J Med* 1932 CCVII 1069  
Acute Pulmonary Congestion and Cardiac Asthma in Patients with Mitral Steno-  
sis" *Am Heart J* 1934 IX 697
- Mackenzie J The Nature and Significance of Heart Symptoms *Brit M J* 1922 I  
505
- Palmer R B and White P D "The Clinical Significance of Cardiac Asthma Review  
of Two Hundred and Fifty Cases" *JAMA* 1929 XCII 431
- Sprague H B "Heart Attacks" *Boston M and S J* 1927 CXCVI 472
- Stokes W Observations on Some Cases of Permanently Slow Pulse *Dublin Quart J*  
1846 II 73  
"On Fatty Degeneration of the Heart: Chapter V of *The Diseases of the Heart  
and the Aorta* Hodges and Smith Dublin 1st ed 1854
- White J C and Smithwick R H *The Autonomic Nervous System Anatomy Physi-  
ology and Surgical Treatment* Macmillan Co New York 2nd ed 1941 (1st ed  
1935)
- White P D and Hahn R G "The Symptom of Sighing in Cardiovascular Diagnosis  
with Spirographic Observations" *Am J M Sc* 1929 CIXXVII 179

---

## CHAPTER 4

---

### PHYSICAL EXAMINATION

#### SIGNS WITH ESPECIAL REFERENCE TO CYANOSIS JAUNDICE AND EDEMA

---

Having obtained the fullest possible information from the patient's own history the physician turns next to the physical examination which fills most of the gaps left in the completion of the picture of the condition of the heart. In the writer's experience the relative values of the different parts of the examination are about as follows: in percentage of the total—history 45 per cent physical examination 25 per cent electrocardiography 15 per cent roentgenology 10 per cent other methods of examination (blood, urine, basal metabolic rate, cardiac catheterization, circulation rate, vital capacity and functional tests) 5 per cent.

There was somewhat of a danger of overemphasis of symptoms and of tests of reserve in the years that followed World War I to the neglect of physical signs. This situation was the result of two factors: in the first place for ten years or more before that war the pendulum had been set swinging from the extreme point of view of the nineteenth century that structural defects and evidence thereof should be the focus of medical diagnosis, prognosis and treatment to the opposite extreme of prime consideration of the functional state of the circulation; and secondly the need of manpower for the armed forces during that war forced disregard for ultimate in favor of immediate prognosis. The situation was more favorable in this respect so far as the U. S. A. was concerned in World War II.

Clues to the etiology of heart disease and to the functional state of the circulation are frequently found in signs other than those presented by the heart directly. It is therefore essential in the physical examination of an individual suspected of having trouble with the heart to search the whole body for such clues. Hence before taking up the examination of the heart itself I shall present the more important signs of heart trouble elsewhere in the body and discuss in somewhat more detail three special conditions—cyanosis, jaundice and edema.

In the first place the general appearance of the patient is of vital importance

this includes age build height and weight (and especially their relationship) nutrition strength mental state color and breathing These various points are often taken in at a glance without careful analysis but they weigh heavily in the final assessment of the case thus affording the physician who personally examines the patient a great advantage over the doctor who is asked to make his diagnosis and prescribe treatment on the basis of hearsay evidence only no matter how careful and detailed may be the history and report of physical signs

**Head and neck** The eyes afford more clues in a cardiac patient than any other part of the body except the neck and the heart itself Exophthalmos and related eye signs suggest at once the probability that at least some of the heart trouble is due to thyrotoxicosis The failure of the pupils to react to light (Argyll Robertson pupil) and their irregularity and inequality indicate at once the need to search for aortitis itself since central nervous system syphilis and cardiovascular syphilis are frequently associated The arcus senilis is not an important clue however it is only a little more common in older individuals with heart disease than in those without The same statement is true of cataracts The eye grounds on the other hand are of considerable importance especially when there is uncertainty about the degree the duration or even the past existence of high blood pressure important hypertension is attended in the course of a few years by sclerosis of the small arteries of the eye grounds which becomes marked in degree and may be attended by edema exudate hemorrhages and even choking of the disks, when the hypertension becomes malignant (Figure 9) Petechial hemorrhages in the conjunctivae are frequently found in subacute bacterial endocarditis

The mouth and throat should be examined for infection of teeth gums and tonsils which may sometimes lead to acute rheumatic heart disease or to acute or subacute bacterial endocarditis in persons susceptible to these diseases (see Chapters 14 and 15)

The neck may show several important abnormalities Thyroid gland enlargement suggests thyrotoxicosis Vigorous arterial pulsation with the subject at rest is indicative of chronic hypertension aortic regurgitation or aneurysmal dilatation A tracheal tug (sometimes called Oliver's sign Oliver 1878) is uncommon when it is clearly evident it points to the presence of an aortic aneurysm Increased activity of the carotid sinus reflex determined by firm pressure exerted by the fingers high up on the carotid artery in the region of the bulb may reveal itself in marked slowing of the heart rate drop in blood pressure or reflex cerebral vasoconstriction with resulting faintness or syncope such a finding may be helpful in explaining symptoms of obscure origin (Weiss and Baker 1933) Finally and most important of all there is engorgement or pulsation of the jugular veins with the subject in the upright position this means most commonly congestive heart failure involving the right ventricle or the whole heart less often it means acute or chronic constrictive pericarditis which blocks the entrance of blood into the heart and least often it indicates organic tricuspid stenosis or regurgitation or obstruc-



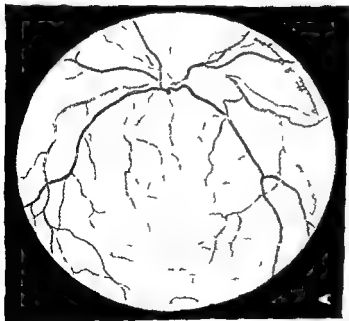


FIG 9 Photographs of the fundus oculi (A) Right eye of a normal blond man age 23 (B) Left eye of a 36 year old blond man with malignant hypertension retinal arteriosclerosis and generalized arteriosclerosis Blood pressure 240 mm mercury systolic and 142 mm diastolic. Albuminuria and granular casts Retinal arteries tortuous irregular in caliber and in various stages of sclerosis Veins are engorged irregularly dilated and markedly compressed by superimposed arteries The superior temporal vein is bordered by white lines Light streaks are increased on the arteries and on the anterior arches of the veins The relatively normal fovea with its reflex resembles the so-called "hole in the macula" owing to surrounding retinal edema Scattered over the fundus there are two kinds of exudates one pale yellowish white solid looking the other (around macula) small superficial white line powdered snow Radiating from the disk in the manner of opaque nerve fibers there are areas of retinal edema stretching into the periphery and in spots obscuring the blood vessels There are many small retinal hemorrhages in various stages of absorption This was a macular condition in the right eye (Kindness of Miss William Whitmore)

tion of the superior vena cava by tumor aneurysm or other mediastinal involvement. The deep systolic jugular pulse should not be confused with the carotid pulse (see Chapter 8).

**Thorax.** Chest deformities have two interesting relationships to heart disease. Precordial bulging of the bony thorax without other important deformities signifies usually the development of cardiac enlargement due to congenital defects or rheumatic involvement during the period of early growth; it is therefore valuable as a sign of important affection of the heart in early childhood. Marked scoliosis and kyphosis may themselves give rise to heart disease or more often to insufficiency of the lungs, and in rare cases a depressed sternum may embarrass the heart (see Chapter 23). Abnormal pulsations and elevations of the chest wall are found in cases of aortic aneurysm (Figure 10) and of cardiac hypertrophy. Palpation of the intercostal spaces



FIG 10 Photograph showing a localized bulging at the right of the upper sternum due to an aneurysm of the ascending aorta and innominate artery

in the dorsal and axillary parts of the thorax may reveal arterial pulsations that indicate the presence of congenital coarctation of the aorta. Cardiac pulsations will be discussed in the next chapter.

Examination of the lungs is of great importance in heart disease. There may be moist rales at the bases due to pulmonary edema resulting from failure of the left ventricle, but such rales must be carefully distinguished from atelectatic rales and from rales due to pulmonary infection or multiple infarction, distinctions which are frequently neglected. Moreover, too much has been made of this sign in contrast to that of simple dyspnea or of emphysema with wheezy respiration due to the more common engorgement of the pulmonary circulation in failure of the left ventricle and in mitral stenosis of high degree. The emphysema in such cases is primarily a functional state and not usually discoverable at postmortem examination when the lung vessels are emptied; it is due to the stiffening of the lung, fixation of the alveoli, and low position of the diaphragm with the result that relatively little air passes in and out and that only with considerable difficulty. Areas of pulmonary consolidation are quite common in heart disease, especially infarcts complicating congestive heart failure or mitral stenosis. These infarcts are due to embolism from venous thrombosis in abdomen, pelvis, or legs (most commonly saphenous and femoral venous thrombosis) resulting from the slowed circulation with or without actual phlebitis and are often serious, occasionally terminal, and frequently overlooked or wrongly labeled pneumonia. Much less commonly such embolism originates from the right heart chambers. Other consolidation of lung tissue may complicate heart disease, especially hemorrhagic involvement in severe active rheumatic infection, and occasionally a real pneumonic process. Finally, signs of hydrothorax in a cardiac patient are common, the result of an active rheumatic pleuritis or a part of a polyserositis which is usually of unknown etiology, or most frequently a transudate due to congestive failure of the right ventricle or whole heart, involving especially the right side of the thorax. Right hydrothorax is more frequent than left, either because of the greater ease of obstruction of the azygos vein on that side, or else because of higher venous pressure in the pulmonary circulation of the right lung than in that of the left lung in congestive heart failure (Dock, 1935; White, August, and Michie, 1947). Ewart's sign (Ewart, 1896; Levine and Gevalt, and Gordon, 1940), consisting of dullness, increased fremitus, and bronchial breathing at the left lung base in cases of pericardial effusion, is probably the result of several factors including compression of the lung by fluid in the pleural as well as in the pericardial cavity and pulmonary infarction.

Interstitial emphysema of the mediastinum (with or without pneumothorax) is revealed by curious crackling sounds heard over the sternum, and sometimes by palpable subcutaneous emphysema in neck or over the anterior thoracic wall (Hamman, 1939; Griffin, 1942).

**Abdomen.** There are three signs obtained by examination of the abdomen that are of significance in a cardiac patient. The first is enlargement of the liver from engorgement due to congestive failure of the right ventricle, to tri-

tricuspid stenosis or to acute or chronic constrictive pericarditis. If the congestion occurs quickly the liver is tender because of the rapid stretching of its capsule. Pulsation of the liver that is easily discernible is rare; it is the result either of advanced congestive failure of the right ventricle with functional tricuspid regurgitation as in mitral stenosis of long standing or of tricuspid valve disease (rheumatic) of high degree. Cirrhosis of the liver may be a coincidental complication of heart disease and failure but in lesser degree it may be a sequel of chronic constrictive pericarditis or mitral stenosis of long standing. The second important abdominal sign in heart disease is splenomegaly which is confirmatory of the diagnosis of subacute bacterial endocarditis. The third sign is ascites (*asaros* bag or bladder) which in a cardiac patient is usually the result of congestive failure of the right ventricle but which may also be caused by tricuspid stenosis or chronic constrictive pericarditis in both of which conditions it more or less parallels the degree of liver engorgement. Ascites may also be a part of a polyserositis (Concato's disease) which forms the background for chronic constrictive pericarditis (Pick's disease) and it may likewise be caused or aggravated by a complicating cirrhosis of the liver. When the possibility of syphilitic aortitis exists inspection of the genitalia for the scar of a chancre may prove helpful.

**Extremities.** Abnormal pulses, dependent edema, cyanosis, clubbing of the fingers and toes, polyarticular rheumatism and rheumatic nodules are the special signs to be looked for here in a cardiac patient. The pulse will be discussed in Chapter 8. Clubbing of fingers and toes associated with cyanosis is found in certain congenital cardiovascular defects (the *morbus caeruleus*) (see Figure 63, page 298). Clubbing without cyanosis is found in subacute bacterial endocarditis. However, it must be remembered that clubbed fingers are often found with noncardiac conditions, most commonly of all in pulmonary diseases; even ulcerative colitis may be the underlying cause and a familial type of unknown etiology has been described. Recently it has been found that in all varieties of simple clubbing except hereditary the blood flows per unit surface or volume of finger tip are abnormally high as the result of reduction of the brachial-digital blood pressure gradients; this increase of blood flow is probably the important factor in the development of the clubbing (Mendelowitz, 1941).

Rheumatic nodules are important evidence of an active rheumatic infection but must be differentiated from the nodes of rheumatoid arthritis (see Figure 84, page 367). It is well also to palpate the dorsalis pedis and posterior tibial arterial pulses; if they are much diminished or absent we have evidence, as a rule, of arteriosclerosis of high degree which may not be limited to the legs or in rare cases of congenital coarctation or of dissecting aneurysm of the aorta. Finally, absence of the knee jerks suggests the need of searching carefully for syphilitic aortitis while their exaggeration points to the presence of a hypersensitive nervous system which may accentuate cardiac symptoms. As a rule the more lively both knee jerks the less serious are the symptoms.

There are three particular signs in a cardiac patient that deserve consideration at some length they are cyanosis jaundice and edema

**Cyanosis** Cyanosis (κίαιος dark blue color) of skin and mucous membranes is a sign much sought for but unless the cyanosis is well marked or constant it may be unimportant since it often results from temporary local disturbances of the circulation and not from serious disease of heart lungs or blood vessels. This change in color is the result of the presence in dilated superficial blood vessels of venous blood in which an abnormally high percentage of the hemoglobin has lost its oxygen (reduced hemoglobin). Two factors are of much importance in determining the degree of cyanosis first the extent of oxygen dissociation or reduction of hemoglobin and second, the degree of dilatation of the blood vessels (arterioles and capillaries) of the skin and mucous membranes which makes the cyanosis visible. The less the oxygen saturation of the hemoglobin and the more dilated the superficial vessels the greater is the degree of cyanosis in any part of the body. Arterial blood should normally be 95 to 100 per cent saturated with oxygen which is equivalent to 19 to 20 volumes per cent (the normal oxygen content of atmospheric air) if it is but 80 to 85 per cent saturated so that it contains 3 or 4 volumes per cent of reduced hemoglobin cyanosis results. The capillary blood should normally contain about 3.5 volumes per cent of reduced hemoglobin if it contains over 6.5 volumes per cent there results a cyanotic color like that of venous blood which normally contains about 6 volumes per cent of reduced hemoglobin. As a rule cyanosis is most common and best seen in lips cheeks ears and hands where the blood vessels are numerous and most exposed to the air. This condition is sometimes called *acrocyanosis* (ἄκρος outermost and κίαιος cyanosis). A further factor in the production of cyanosis is the amount of hemoglobin in the blood with an increased amount as in polycythemia the blood possesses a much more pronounced blueness of color due to the high total content of reduced hemoglobin than when there is dilution as in anemia even though the percentage of reduction of the hemoglobin is the same.

The underlying causes of cyanosis are seven

- 1 The first and most common factor is local and consists of the slowing of the peripheral circulation by cold or vasomotor nervous stimulation. Arterial vasoconstriction reduces the capillary blood pressure and speed of flow. This slowed circulation of the blood allows a greater dissociation of oxygen than usual hence the cyanosis. If the cold becomes intense however the dissociation of oxygen stops and even though the circulation remains very slow the skin color is red and not blue due to the presence of arterial blood. An abnormally high degree of sensitiveness to cold especially in the hands with the paroxysmal production of cyanosis (or pallor) is seen in the condition called Raynaud's disease (see Chapter 31). The high degree of circulatory disturbance in this condition is usually attended by pain. Probably both cold and vasomotor nervous stimulation act together in Raynaud's disease.

2 Obstruction to the return of blood to the heart may also cause cyanosis either from internal cause namely congestive failure of the right ventricle tricuspid stenosis or acute or chronic constrictive pericarditis or from local causes namely pressure on the veins by tumor or constriction venous thrombosis or incompetent venous valves The slowing of the blood flow through the vessels of the skin causes increased dissociation of oxygen and a blue color exaggerated by capillary dilatation

3 A third very important factor is congestion of the lungs due to heart trouble A chronic engorgement of the lung vessels in mitral stenosis or acute or chronic engorgement from failure of the left ventricle causes a certain amount of blood to pass through the lungs in the middle of the dilated capillaries and so out of contact with the alveolar air continuing into the systemic circulation as venous or blue blood with a considerable dissociation of oxygen If enough of the blood one third it has been estimated is so shunted from venous system to arterial system cyanosis will result Often combined with this factor of engorgement of the lung vessels is that of slowing of the return of blood to the heart from various causes Thus one factor may reinforce another in the production of cyanosis

4 Certain congenital heart defects may cause cyanosis by shunting venous blood directly into the systemic circulation via a single ventricle or dextroposed aorta overriding both ventricles or in transposition of the great vessels or less commonly and later in life through interventricular or interatrial septal defects or patent ductus arteriosus It has been calculated that 30 to 40 per cent of the venous blood must be so shunted in order to assure the presence of cyanosis In patients of this type the capillaries of the skin have been found dilated and the peripheral circulation slowed and it has been suggested that this local factor may be more important in the production of cyanosis than the congenital heart disease itself It is likely however that the veno arterial shunt alone is responsible for most of the cyanosis which is in turn deepened or perhaps even brought to notice by the slowing of the peripheral circulation the slowing of the peripheral circulation is occasioned by the need of the tissues to remove sufficient oxygen from the oxygen deficient blood stream The polycythemia present in most cases of congenital heart disease with a right to left shunt is an additional factor which exaggerates cyanosis Congenital heart defects in which there is no veno arterial shunt are not attended by cyanosis unless there is a complicating factor of congestive heart failure or pulmonary disease

5 Disease of the lungs acute or chronic may be a cause of cyanosis the presence and degree of which are dependent on the amount of pulmonary involvement and on the presence of complicating factors With consolidation of much lung tissue in pneumonia or infarction venous blood in sufficient amount to cause cyanosis is shunted through the pulmonary circulation without coming into contact with alveolar air Moisture in the alveoli and bronchioles may act even more than consolidation to cause cyanosis by preventing contact of blood with air as is the case with severe influenza or

inversely but not in the same degree. In nephrosis and starvation edematous fluid is very low in protein giving percentages lower than in any other conditions while the fluid from lymphedema and also from edema in inflammatory areas has a high content of protein the more purulent the inflammatory edema is the higher its protein content and the nearer it approaches the chemical state of blood serum. The specific gravity of edematous fluids varies with the protein content from about 1.008 with very little protein to 1.020 or more approaching the specific gravity of blood serum itself. Ascitic and hydrothoracic fluids or so called transudates in congestive heart failure have the same composition as subcutaneous edema fluid except for a somewhat higher protein content and a higher specific gravity (about 1.012).

Most of the underlying causes of edema are known. In the first place there is the simple effect of gravity. Standing long in one position with little or no movement of the legs (contraction of the leg muscles favors an upward flow in the veins) causes a slowing of the circulation with increase in size of the legs from stasis progressing in extreme cases to actual edema which is usually most evident in the ankles just above the shoes and over the shins. This edema becomes palpable it is said when the limb volume has increased by 8 per cent. The heavier the person and the longer the time on the feet the more likely is the appearance of edema. This edema may be regarded as a physiologic occurrence when it is found in heavy persons who stand much of the time. Walking or other movement of the feet and legs aids the circulation and tends to prevent edema. The presence of varicose veins favors its occurrence especially unilaterally or preponderantly in one leg or the other.

Besides gravity a common cause of edema and one of the most frequent is obstruction to the return flow of fluid from tissues to heart. Lymphatic block is rarely the cause of any important edema although it may in exceptional cases give rise to chronic massive increase in size of legs or arms or genitalia called elephantiasis. Obstruction of the venous circulation is frequently responsible for edema. This obstruction may come in a variety of ways (1) by venous thrombosis due to inflammation or to stasis (2) by pressure on veins from without by tumors scars and tight bands and more or less normally late in pregnancy (in the last four weeks) and (3) by resistance to the flow of blood into the heart usually because of the inability of the right ventricle from failure or otherwise to pass on all the blood it receives. This venous obstruction also may be due to tricuspid stenosis or to limitation of the size of right heart chambers and venae cavae by a large pericardial effusion or by chronic constrictive pericardial adhesions (as in Pick's disease) so that too small an amount of venous blood enters the heart in diastole with resulting accumulation of edema fluid in tissues and serous cavities. The explanation of edema secondary to obstruction of the return flow of blood to the heart from any cause is the increased hydrostatic pressure in the venous ends of the capillaries which results from the increased pressure in the systemic veins and which prevents the normal absorption of fluid from the tissues. Krogh, Landis and Turner (1932) demonstrated that excessive

fluid accumulates in the tissue spaces in man when the venous pressure (normally 6 to 8 cm of water) is raised above 15 to 20 cm

Another important type of edema but much less common than that resulting from venous obstruction with or without cardiac cause is that dependent on physiochemical factors which produce a disturbance of the normal osmotic pressure relationship between the fluids in capillaries and tissues. Here disorders of either liver or kidneys may play an important role with the onset of a spontaneous diuresis heralding a beginning recovery. The higher concentration of substances in particular proteins which diffuse with difficulty through the capillary wall in the blood stream than in the body tissues establishes an osmotic pressure which normally draws fluid from tissues into the blood and so tends to neutralize the hydrostatic pressure so far as the fluid balance on both sides of the capillary walls is concerned. Nephritis especially with nephrosis and disturbances of tissue metabolism due to starvation are frequently associated with edema. This edema is usually general in distribution affecting face, arms and hands and not simply the dependent portions of the body as in congestive heart failure. Nephritic edema is due fundamentally to damage to the renal tubules which prevents the concentration of the urine and the reabsorption of albumin. The low content of albumin in the capillary blood serum prevents the proper return flow of fluid by osmotic pressure into the blood from the tissues. A certain type of nephritis with free loss or leakage of sodium tends like Addison's disease with its faulty sodium metabolism toward dehydration and collapse and not edema.

Edema secondary to decreased negative osmotic pressure of the blood may be added to edema due to increased positive hydrostatic capillary pressure in a patient with congestive heart failure and malnutrition. This is a point of much importance and explains obscure findings in some cases. The excessive ingestion of sodium chloride particularly in cases of low myocardial reserve also favors the accumulation of edema in the body tissues.

Another important cause of edema in congestive heart failure seems to be due to deficient circulation to the kidneys secondary to failure of the myocardium of the left ventricle or of the whole heart and resulting in inability of the kidneys to excrete sodium normally. The retention of sodium results in the building up of the body water both in and out of the circulation.

Recently Sarnoff (personal communication 1951) has found that in experimental animals excessive stimulation of the vasomotor center in the brain can result in such peripheral vasoconstriction that blood is rapidly transferred in bulk from the systemic circulation to the pulmonary circulation resulting in pulmonary edema. This is probably an explanation for the so-called neurogenic or cerebral type of pulmonary edema.

The metabolic disorder of hypothyroidism (myxedema) is commonly associated with a nonpitting accumulation of fluid in the body tissues generally (not primarily in dependent parts of the body) and is attended by a low blood plasma volume in contrast to cardiac edema. Thyroid therapy clears this myxedema.



Beriberi (avitaminosis) is attended by the accumulation of fluid in body tissues but rarely by frank edema

A rare type of edema of unknown cause is hereditary in nature (Milroy 1892 Braham and Howells, 1948)

There are two other varieties of edema that need little comment here because of their ease of recognition and their absence of connection with cardiovascular disease (1) local tissue edema associated with an infectious or toxic process the commonest kind of edema of all and (2) angioneurotic edema (Quincke 1882) also generally localized

Edema due to heart disease may be of any degree from slight edema of the lungs or over ankles or shins developing after a considerable length of time in the standing position to massive edema (called *anasarca* also upon or throughout and *oedema* flesh) of much of the body in extreme cases even affecting the arms chest wall and face With extensive cardiac edema fluid tends to accumulate also in the peritoneal cavity (ascites) pleural cavities (hydrothorax) especially the right where it appears earlier than in the left and even in the pericardium (hydropericardium) Edema of one side of the body (as of face arm chest abdominal wall or leg) may sometimes be more marked than that of the other side it may be found that this is the effect of gravity the patient having been lying on that side of the body When however in an ambulatory patient edema is confined to one leg or is much more marked in one leg than in the other local venous obstruction (or vasodilatation) is the probable cause Cardiac edema may be associated with some other type of edema in the same case

Edema of the brain is the result of infection hemorrhage infarction or toxic influences such as alcoholism its occurrence in heart disease is not clearly recognized even when there is extensive anasarca involving the upper part of the body in the course of extensive congestive heart failure Edema of lungs may be found in noncardiac patients as the result of infection infarction nephritis or toxic state or as an unusual reflex to pleural trauma or to central nervous system disease when of cardiac origin it results from failure of the left ventricle or from obstruction to the entrance of blood into the left ventricle by marked stenosis of the mitral valve It is to be noted that pulmonary edema is due to left ventricular failure and not to right ventricular failure in fact when right ventricular failure follows failure of the left ventricle as often happens, congestion and edema of the lungs decrease and sometimes disappear entirely Edema of the liver and other abdominal and pelvic viscera is commonly due to failure of the right ventricle or of the whole heart to marked tricuspid stenosis or to acute or chronic constrictive pericarditis Edema of heart and skeletal muscle is not common it has been noted in extensive general anasarca and in beriberi

Finally it is to be noted that bilateral pitting edema of the legs is much less commonly due to heart failure than to other causes especially local venous circulatory fault even in cardiac patients themselves Much digitalis has been wastefully prescribed in such cases before careful appraisal of the heart itself

has demonstrated its futility in these patients of course heart failure may by chance eventually supervene and then digitalis may clear the new increment of edema

## BIBLIOGRAPHY

SIGNS WITH ESPECIAL REFERENCE TO CYANOSIS JAUNDICE AND EDEMA

SEE ALSO GENERAL REFERENCES AFTER CHAPTER 2

- Braham J and Howells G Hereditary Oedema (Milroy's Disease) *Brit M J* 1948 I 830
- Dock W The Anatomical and Hydrostatic Basis of Orthopnea and of Right Hydrothorax in Cardiac Failure *Am Heart J* 1935 X 1047
- Drinker C K, Field M E and Homans J Experimental Production of Edema and Elephantiasis as a Result of Lymphatic Obstruction *Am J Physiol* 1934 CVIII 509
- Elias H and Feller A *Stauungstypen bei Kreislaufstörungen Mit besonderer Berücksichtigung der exsudativen Perikarditis Eine anatomische experimentelle und klinische Untersuchung* Julius Springer Vienna and Berlin 1926
- Ewart, W Practical Aids in the Diagnosis of Pericardial Effusion *Brit M J* 1896 I 717
- Footo S A Jr, Reed W C, Comeau W J and White P D The Clinical Significance of Bilateral Edema of the Lower Extremities *Am J M Sc* 1940 CXCIX 512
- Griffin R J "A Diagnostic Sign of Spontaneous Interstitial Emphysema of the Mediastinum" *Ann Int Med* 1942 XVII 295
- Hamman L Spontaneous Mediastinal Emphysema *Bull Johns Hopkins Hosp* 1939 LXIV 1
- Keefer C S and Resnik W H Jaundice Following Pulmonary Infarction in Patients with Myocardial Insufficiency I A Clinical Study *J Clin Investigation* 1976 II 375 II An Experimental Study *Ibid* p 389
- Krogh A, Landis E M and Turner A III The Movement of Fluid Through the Human Capillary Wall in Relation to Venous Pressure and to the Colloid Osmotic Pressure of the Blood *J Clin Investigation* 1932 XI 63
- Levine M A and Gevalt F C Jr with discussion by Gordon A H The Significance of Ewart's Sign *Tr A Am Physicians* 1940 LV 106
- Lundsgaard C and Van Slyke D D "Cyanosis" *Medicine Monographs* Williams and Wilkins Co Baltimore 1923
- Meakins J "The Distribution of Jaundice in Circulatory Failure" *J Clin Investigation* 1927 IV 135
- Mendlowitz M Measurements of Blood Flow and Blood Pressure in Clubbed Fingers *J Clin Investigation* 1941 XX 113
- Milroy W F "An Undescribed Variety of Hereditary Oedema" *New York M J* 1892 LVI 505
- Oliver W S "Physical Diagnosis of Thoracic Aneurysm" *Lancet* 1878 II 406
- Quincke H I "Über akutes umschriebenes Hautödem" *Monatsch f prakt Dermat* 1882 I 129
- Sarnoff S J Massive Pulmonary Edema of Central Nervous System Origin Hemodynamic Observations and the Role of Sympathetic Pathways *Federation Proc Fed Am Soc of Exper Biol* 1951 X 118
- Stead E A Jr Edema of Heart Failure *Bull New York Acad Med* 1948 XXIV 607
- Weiss M and Baker J P Carotid Sinus Reflex in Health and Disease Its Role in Causation of Fainting and Convulsions *Medicine* 1933 XII 297
- White P D, August M and Michie C R Hydrothorax in Congestive Heart Failure *Am J M Sc* 1947 CCXIV 243
- Yountans J B, Bell A, Donley D and Frank H Endemic Nutritional Edema I Clinical Findings and Dietary Studies *Arch Int Med* 1932 I 843

---

## CHAPTER 5

---

# PHYSICAL EXAMINATION OF THE HEART ITSELF

---

### INSPECTION PALPATION PERCUSSION AND AUSCULTATION

This chapter and the next along with Chapters 3 and 4 concern themselves with the simplest and yet the most fruitful methods of examination requiring only the use of the voice the ears the eyes the fingers the stethoscope the blood pressure instrument and especially the intelligence all of which are at once available to the practicing physician Time and effort supply the necessary experience

One is very prone in these days of the machine age to abandon the patient training and skilled use of the unaided senses Nowhere is this truer than in the practice of medicine It has become rather too easy in hospitals or even in the doctor's office to make a roentgen ray examination of the heart and to neglect inspection palpation and percussion But the senses of sight touch and hearing unaided by instruments except for the simple convenience of a stethoscope and of a sphygmomanometer are still well worth cultivating When the senses are highly trained and skillfully used they establish such a justified feeling of confidence that it is possible to obtain much information about heart size and shape even when the roentgen ray is not available and also to secure other important data about the heart not shown by the roentgen ray as in the case of palpable thrills and changes in heart sounds and the presence of murmurs which reveal much concerning the structural changes in the heart and its functional condition

### INSPECTION AND PALPATION

*The first important thing to attempt to do on examination of the heart is to locate the position of the apex best done with the subject seated and the thorax inclined slightly forward This is possible in the great majority of cases failing only in a few obese or very sick patients Both inspection and palpation aid in this purpose but more especially palpation which by the use of the trained fingers permits the identification of the maximal impulse as the site of the cardiac apex Such identification is usually in agreement within a few*

millimeters with the position of the apex as determined by orthodiagraphy. A measurement of the horizontal distance of the maximal apex impulse from the midsternal line tangentially to the front of the chest is recorded in centimeters and compared to the position of the midclavicular line which is a vertical line dropped from a point halfway between the midsternum and the outer end of the left clavicle as noted below (Figure 11). The position of the cardiac apex should lie in the left fifth intercostal space in or to the

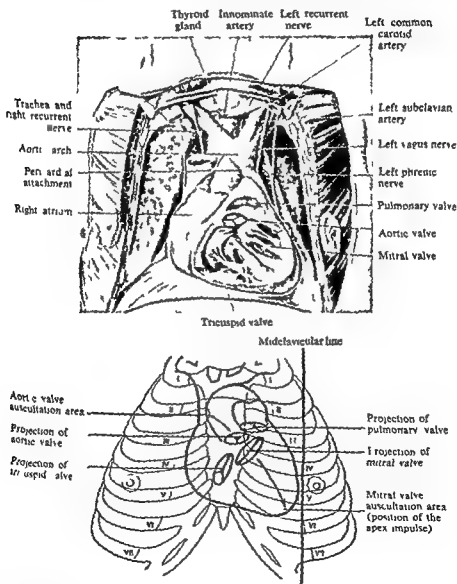


FIG 11 Topographic relationships of the heart and great vessels. The heart chambers and blood vessels are shown in a distended state. (Corning *Lehrbuch der topographischen Anatomie* 1917.)

right of the midclavicular line in a normal adult sitting or standing except in rare instances when the heart may be displaced upward and a little outward from great abdominal distention as in pregnancy. The average position of the midclavicular line in the normal adult is 8 to 8½ cm to the left of the midsternum varying from 7 to 10 in the extremes of body size. The maximal apex impulse falls normally on this line or ½ to 1 cm within it rarely when the thorax is long and the heart vertical in position so that it is almost centrally placed in the chest the cardiac apex is low often behind the sixth rib or rarely in the sixth intercostal space and as much as 1½ to 2 cm medial to the midclavicular line. If it is beyond the midclavicular line in the fifth space enlargement of the heart is to be diagnosed unless the heart is displaced by fluid or air in the right pleural cavity by a depressed sternum or by retraction of the left lung and pleura. If the heart is displaced upward appreciably its apex tends to lie in the fourth intercostal space or behind the fifth rib and may then be normally slightly (½ to 1 cm) beyond the midclavicular line. In infants and very young children especially when they are fat the apex impulse is normally often in the fourth intercostal space just beyond the midclavicular line.

Certain changes of body position and of the height of the diaphragm cause considerable shifting of the position of the apex impulse when the heart is normally freely movable. The three greatest shifts are produced as follows: (1) a change from the left to the right lateral decubitus causes a shift of the mediastinum and its contents including the heart laterally, the cardiac apex impulse moving often as much as 4 or 5 cm from left to right, from out toward the anterior axillary line to a point not far to the left of the sternum, such a shift does not markedly affect the angle of either the anatomic or the electric axis and so produces little change in the electrocardiogram which in part explains why such a test of change of position is of little value in the diagnosis of adhesive pericarditis. (2) A change in the height of the diaphragm produced readily by deep breathing alters appreciably the position of the apex impulse both laterally and vertically from say a point in the midclavicular line underlying the fifth rib to a point 1 to 1½ cm inside the midclavicular line underlying the sixth rib such a shift does markedly affect the angle of both anatomic and electric axes of the heart and so produces usually a striking change in the electrocardiogram particularly in Lead 3 (see Figure 4 page 33). (3) A change from the supine to the standing position alters somewhat the position of the apex impulse partly by straightening out the heart (that is in slight to moderate degree making it more vertical), partly by producing a rotation from left to right and partly by causing a drop of the heart as a whole the result is somewhat like that caused by deep inspiration but not so pronounced and more complicated in mechanism the effect on the electrocardiogram is very variable but usually not marked (see Chapter 9).

Finally it is to be noted that the nipple line is not a suitable guide to heart size chiefly because of its great variation in distance from the midsternum in

individuals of the same size (as much as 2 or 3 cm in extreme cases) but also because as a rule its position is normally 1 to 2 cm beyond the site of the cardiac apex

*The major pulsatory movements of the thoracic wall* which may be seen and felt resulting from the action of an enlarged heart are often complicated but their analysis may aid in elucidating the heart condition they have been made the subject of a monograph by Dressler (1933 and 1937) A few major points of interest are the rocking movement of the thorax when the left ventricle is very large and forceful the left thoracic wall moving outward and the right inward in systole and vice versa in diastole the forward thrust of the anterior thoracic wall with retraction of both lateral walls in systole when the right ventricle is very large and strong together with a visible and palpable forceful impulse in the region of the pulmonary artery in some such cases when the chest wall is not too thick and an outward thrust of the right chest wall in systole when the atria are markedly enlarged as in the case of the occasional huge left atrium found in advanced mitral valve disease and of the large right atrium in tricuspid valve disease the outthrust being due not to atrial contraction but to the forceful ventricular pulse transmitted directly into the atrium through the incompetent valve These are more or less major pulsatory movements in addition to the apex impulse itself When the heart is much enlarged and its action forceful the fifth and sixth ribs are outwardly displaced at each heart beat

Two other points about cardiac pulsation are worthy of comment First a very active heart whether enlarged or not will produce such a forceful apex impulse that it is widely felt and may be misleading it is the maximal point of this impulse or rather a few millimeters beyond but not its furthest point out that marks the position of the apex itself Second a systolic retraction of the fourth and fifth intercostal spaces just to the left of the sternum often well seen in a person with a thin chest wall is a normal occurrence when the heart is not enlarged or when only the left ventricle is enlarged and it is not to be interpreted as the result of pericardial adhesions it is due to the withdrawal of the right ventricle from the chest wall when it contracts against the left ventricle which in turn contracts away from the region of the sternum but thrusts its apex up against the chest wall further to the left that is in or beyond the midclavicular line depending on the size of the left ventricle

*Thrills* The next observation to make in physical examination of the heart is to palpate the precordium for thrills which are often difficult to feel with the untrained hand unless they are very marked in degree exercise by increasing heart action and blood flow helps to make thrills that are faint more evident when a thrill is suspected and is not brought out by exercise it probably does not exist Thrills are relatively rare accompanying a few murmurs only especially the aortic systolic murmur of aortic stenosis and the mitral diastolic murmur of mitral stenosis Valvular regurgitation produces thrills in only the rarest cases whether from aortic regurgitation mitral regurgitation or pulmonary regurgitation and then usually when the valve has an odd deformity

such as eversion or rupture of an aortic cusp or a rupture of mitral cusp or of chordae tendineae

A systolic thrill felt over the precordium but best in the second intercostal space just to the right of the sternum (so-called aortic valve area) and transmitted into (but not limited to) the vessels of the neck is due as a rule to aortic or subaortic stenosis rarely to an aortic aneurysm, it is of interest and importance that such a thrill may be felt well also at the cardiac apex. A systolic thrill, felt usually in a narrowly localized area in the second intercostal space just to the left of the sternum (so-called pulmonary valve area) means in most instances congenital stenosis of the pulmonary valve or of the infundibulum of the right ventricle rarely patency of the ductus arteriosus or extreme dilatation of the pulmonary artery. A systolic thrill also usually very limited in extent felt in the fourth intercostal space just to the left of the sternum indicates as a rule the presence of an interventricular septal defect. A diastolic thrill middiastolic or presystolic in time felt in a small area at the cardiac apex and a little toward the midsternum from the apex is characteristic of a high degree of mitral stenosis but is also found in rare cases of marked dilatation of the left ventricle with rapid blood flow (see Chapter 14). A continuous thrill rather rare felt in the second intercostal space just to the left of the sternum is found in a few cases of patency of the ductus arteriosus or to the right in the extremely rare instances of right aortic arch or dextrocardia plus patency of the ductus arteriosus such a thrill is also characteristic of an arteriovenous communication (called aneurysm) anywhere in the body.

Finally it should be noted that the search for thrills may be misleading for three important reasons (1) they may not be felt even in the presence of loud and important murmurs as for example in some cases of aortic stenosis (2) they may be suspected when there is actually nothing wrong and (3) they may be felt in almost unique cases where no murmur can be heard due to the inaudibility of vibrations of very low pitch which are nevertheless of importance.

## PERCUSSION

Before turning to the subject of cardiac auscultation later in this chapter I welcome the opportunity to say a few words about the much neglected and often despised method of cardiac percussion (*percutere* to strike). Percussion of the heart is valuable in the first place because it aids in determining heart size and shape when it is not possible to carry out a roentgen ray study a procedure that continues to be difficult or impossible in the case of quite a few patients. Secondly it is of help in occasional cases when the apex impulse is felt with difficulty or not at all. And thirdly it serves as a check on the accuracy of reports of roentgen ray measurements. Considerable training and experience are necessary before one can properly rely on the accuracy of cardiac percussion but such training and experience are not difficult and

they are well worthwhile. The method of percussion matters little that is whether direct (immediate) or indirect (mediate) whether one uses the finger or special instrument as the pleximeter and whether a hard stroke or a gentle stroke is employed (a light stroke is preferable when the chest wall is thin and the heart near to its surface and a heavier stroke when the chest wall is thick or some emphysema of the lungs is present). The main point is to adopt a definite technic and to stick to it until one becomes expert in its use constantly comparing at first the results obtained with the heart measurements by orthodiagram. Percussion involves not only the sense of hearing but also that of touch.

Auenbrug er Leopold *Inventum Novum Ex Percussione Thoracis Humani*  
Vienna 1761

From John Forbes English translation 1824

I The thorax of a healthy person sounds when struck

II The sound thus elicited from the healthy chest resembles the stifled sound of a drum covered with a thick woollen cloth or other envelope

III Over the space occupied by the heart the sound loses part of its usual clearness and becomes dull

IV The thorax ought to be struck slowly and gently with the points of the fingers brought close together and at the same time extended

Scholium Robust and fat subjects require a stronger percussion such indeed as to elicit a degree of sound equal to that produced by a slight percussion in a lean subject

X To be able justly to appreciate the value of the various sounds elicited from the chest in cases of disease it is necessary to have learned by experience on many subjects the modifications of sound general or partial produced by the habit of body natural conformation as to the scapulae mammae the heart the capacity of the thorax the degree of fleshiness fatness and so forth

XLVI Signs of Hydropericardium The sound in the cardiac region is now as completely deadened as if the percussion were applied to a fleshy limb

XLVIII When the heart becomes so much distended by blood accumulated in its auricles and ventricles as to be unequal to propel forward its contents it frequently becomes thereby enormously dilated. This dilatation has been called Aneurism of the Heart

The pathognomonic sign of this affection is the complete fleshy sound on percussion existing over a considerable space in the region of the heart

In the course of one's palpation and percussion one may elicit an important symptom namely *precordial tenderness* which in the absence of local trauma or lesion of the chest wall itself is useful evidence of a high degree of nervous sensitivity or fatigue as in cases of neurocirculatory asthenia it is found usually in the absence of heart disease (see Chapter 22)

It is well to percuss first the cardiac apex beginning in the left axilla and working toward the sternum. One observes a pronounced change of note and resistance when one reaches the apex (usually 7 to 9 cm to the left of the



midsternum in the normal adult) and this point agrees within a centimetre with that of the *maximal apex impulse* it tends to be a few millimeters further to the left. It is to be compared as is the site of the apex impulse with the midclavicular line. Next it is best to percuss the left border of the heart in the third and fourth intercostal spaces. an increase of heart size towards the left is usually made out readily and here again there is close agreement as a rule between percussion and orthodiagraphic measurements.

Percussion dullness in the third intercostal space to the left of the sternum should not normally exceed one half the distance from midsternum to apex (that is not more than  $3\frac{1}{2}$  to  $4\frac{1}{2}$  cm according to the size of the individual) it often measures less. If it does exceed this we have evidence of abnormality in heart size or shape or both. It may be too far to the left even when the apex impulse is in the normal position such a finding is usually indicative of mitral stenosis, an atrial septal defect or congenital patency of the ductus arteriosus. for the measurement records the size of the left atrium near its appendage and of the trunk of the pulmonary artery.

The reason why the left border of the heart can be so well percussed in most cases is because it lies close to the anterior chest wall especially in the sitting and standing positions. Obesity and pulmonary emphysema and rarely widely transmitted abdominal tympany may interfere with percussion of the heart.

We find a very different situation when we try to percuss the great vessels in the first and second intercostal spaces to left and right of the sternum and under the upper sternum itself. It is difficult or impossible to outline these structures when they are normal and sometimes even when they are enlarged because of their small size, their distance from the anterior chest wall and their proximity to resonant air passages and lung apices. Only when there is a pronounced abnormality as in the case of an aortic aneurysm does one find increased dullness by percussion to the right or left of the upper sternum respectively. It is generally convenient to make a record that there is no abnormal dullness in the region of the great vessels except in the infrequent cases where there is such abnormal dullness rather than to attempt to distinguish doubtful percussion borders. The same is true of percussion of the right side of the heart in the attempt to outline the position of the border of the right atrium, it is impossible to percuss accurately this heart border because of its distance from the anterior chest wall there being an error of 1 to  $1\frac{1}{2}$  cm under the best of circumstances (the right border of the right atrium in the normal adult is usually about 4 cm to the right of the midsternum while the dullness by percussion extends only 2 to  $2\frac{1}{2}$  cm to the right just barely beyond the right edge of the sternum). Clearly defined dullness to percussion in the third and fourth intercostal spaces more than a centimeter to the right of the right edge of the sternum almost always means enlargement of the heart in whole or in part or displacement of the heart to the right or a pericardial effusion rarely this may be found normally when the chest wall is very thin. As a rule therefore it is convenient to say that there is no ab-

normal dullness to the right of the sternum when such is true rather than to give measurements which are misleading as to actual heart size

Finally we need no longer trouble with the old designations : absolute and relative cardiac dullness : they serve no useful purpose

## AUSCULTATION

Laennec R T H *De l'auscultation mediate* Paris 1819 Brief extracts translated by myself

About three years ago I began the research the result of which I am publishing today

Some physicians have tried to apply their ears to the precordial region in these cases The heart beat perceived thus simultaneously by the senses of hearing and of touch becomes more evident This method is however far from giving the results it would seem to promise I have found it advised nowhere As uncomfortable for the physician as for the patient the method is so disagreeable that it is practically of no use in the hospitals it is hardly to be suggested in the case of most women and in some of them it cannot be employed at all because of the size of the breasts

I was consulted in 1816 by a young woman who presented general symptoms of heart disease and in whose case the application of the hand and percussion gave little information because of her obesity Since the age and the sex of the patient forbade my using the method of examination already described (that is immediate auscultation) I happened to recall a well known acoustic phenomenon if one applies the ear to one end of a beam one hears very distinctly a pin scratch at the other end I thought that I could profit by this physical property in the case of the patient under discussion I took a sheet of paper rolled it up tightly applied one end of this cylinder on the precordial region and placing my ear against the other end I was as surprised as pleased to hear the heart beat in a manner much more clear and distinct than I had ever done by applying the ear immediately to the chest

I use at present a cylinder of wood pierced in its centre by a tube three lines in diameter and divided in the middle by a screw joint in order to make it more portable

Auscultation of the heart (*auscultare* to listen) has become a time worn method of examination and is considered by some to be old fashioned and unworthy of especial attention but it remains today a source of vital information about the heart and it has actually advanced in importance in the last two decades because of the better understanding of its findings Like percussion it demands careful training and long experience for its mastery but the time spent on it is exceedingly worthwhile Because of our present knowledge about heart sounds and murmurs even direct or immediate auscultation may be practiced with far better success than in the days before Laennec introduced the stethoscope for indirect or mediate auscultation in 1819 but the use of the ear directly applied to the chest is clumsy and inconvenient and does not allow the detection of the fine shades of tone and intensity that is

possible by the use of a stethoscope. The most useful instrument is binaural with two easily adjustable chest pieces—one a bell and the other a flat resonating chamber with diaphragm (Bowles chest piece) which have a somewhat selective action. For physicians who are hard of hearing and for amphitheater clinics, audition tube amplifiers are now available. With earphone connections there is very little distortion of sounds and murmurs; this method has proved to be well worthwhile in demonstrations to large groups during the past few years.

Auscultation of the heart should be carried out at the cardiac apex (mitral valve area) in the second intercostal space just to the right of the sternum (aortic valve area) in the second intercostal space just to the left of the sternum (pulmonary valve area) at the left of the mid and lower sternum (septal and tricuspid valve areas) and in the left axilla, lung bases and neck for transmission of murmurs. Both bell and Bowles chest pieces should be used, and if there is any possibility of mitral stenosis and the murmur thereof is not heard with the subject in the upright position it should be sought with the subject supine or lying on the left side and after exercise. It is also worthwhile to listen routinely over the thoracic spine in a search for the continuous murmur caused by coarctation of the aorta.

An interesting application of the principle of selective binaural timing of sounds and murmurs to ascertain their points of origin and directions of transmission for example from cardiac base toward apex or vice versa has been introduced and perfected by Kerr and his associates (1937). This acoustic principle is similar to the optic recognition of distances and timing by binocular perspective vision. The instrument devised for this purpose has been called the symballophone and can be used helpfully provided the hearing is equal in both ears (they should be accurately tested) and provided experience in the use of the symballophone is gained by practice. Inertia has delayed any general adoption of this innovation.

*Phonocardiography* (also called stethography in the past) the graphic recording of heart sounds and murmurs by electric reproduction using microphone amplifier and galvanometer has gradually reached a good state of development during the past generation and can usefully supplement the personal use of a stethoscope by a trained observer especially in the exact timing of sounds and murmurs in problem cases. Two difficulties have yet to be eliminated: the first that of the frequent addition of artifacts from extraneous sounds or electric currents to the heart sound records; and second that of the sometimes inadequate reproduction of certain murmurs especially the fainter diastolic murmurs of low or high pitch. However, these difficulties have been largely surmounted. One additional benefit may eventually accrue through this technical method of study, namely extra information about the state of the heart from variations in inaudible vibrations picked up by the apparatus but which have not as yet received adequate clinical analysis. Classroom amplification of heart sounds and murmurs by the additional use of a loud speaker needs further perfection.

There were published some years ago (Rappaport and Sprague 1941 and 1942) two interesting and valuable papers on the physiologic and physical laws that govern auscultation and their clinical applications with especial reference to phonocardiography their conclusions are worthy of direct quotation Their 1941 paper was summarized as follows

Rappaport Maurice II E E and Sprague Howard II M D : Physiologic and Physical Laws that Govern Auscultation and Their Clinical Application *Am Heart J* 1941 XXI 257

"1 Tones of different periods of oscillation or frequency but of similar intensity affect the human ear to different degrees The audiogram which is a graphic representation of the threshold of audibility is a measurement of the degree to which human hearing varies with respect to the frequency of vibration of the stimulus

"2 The minimum change in intensity of a sound stimulus to which the human ear is capable of responding varies with the general level of the sound as well as with its frequency In the auscultatory frequency band as the frequency of the stimulus is lowered a decidedly greater percentage variation in intensity is therefore required to produce the minimum perceptible change

"3 The human ear is a better detector of changes in frequency than of changes in intensity A sound stimulus with a high sensation level requires less of a frequency variation to produce minimum susceptibility than does a sound stimulus of a lower sensation level Also the ear is somewhat less sensitive to frequency variations at the lower end of the auscultatory frequency band than it is to variations in the upper region

4 In the auscultatory frequency band the frequency of a stimulus may be varied rapidly over a considerable portion of an octave without detection by the ear

5 The auditory sensation produced by a complex sound may be decidedly different in character as well as in intensity when the stimulating level is decreased or increased even though no distortion is introduced As a complex sound such as a murmur becomes more intense the low pitched components appear more prominent to the observer

6 When a sound of comparatively high intensity immediately precedes a sound of considerably lower intensity masking of the sound of lower intensity may result.

7 There are many paths along which heart and chest sounds travel in the human body in order to reach the surface As a result a large percentage of the sound energy never reaches the surface because of viscosity elasticity density spreading reflection and refraction losses

8 The entire auscultatory frequency band for heart sounds and murmurs lies below 1 000 cycles per second An estimation of the lower frequency limit of heart sounds and murmur components puts it in the vicinity of 5 to 10 cycles per second although 30 to 40 cycles per second is the lower limit of audibility

9 Acoustic stethoscopes may be classified as either monaural binaural or differential Either the monaural or binaural stethoscope may be employed for general auscultatory purposes whereas the differential stethoscopes are primarily instruments for localizing and comparing sounds

10 The open stethoscopic chest piece or bell when applied to the patient's

chest may be considered as a diaphragm type of chest piece. The skin which is bounded by the lip of the bell forms the diaphragm and the fleshy portion under the skin acts as a damping medium.

11 The larger the diameter of the open stethoscopic chest piece the better its response to low pitched sounds. This is accomplished at the expense of the higher frequency components.

12 The greater the pressure with which the open stethoscopic chest piece is applied to the patient's chest the better is the response of the stethoscope to higher frequency components. Thus by varying the application pressure the physician exerts a variable filtering action upon the sounds because the natural period of the skin diaphragm bounded by the chest piece depends on the application pressure.

13 Open stethoscopic chest pieces of various geometrical shapes have been devised to improve the sound accumulating efficiency of the stethoscope. A bell with its interior shaped like a parabola has been a favorite. Such chest pieces invariably decrease the efficiency of the stethoscope because they increase the internal volume of the chest piece.

14 The only important consideration when designing an open stethoscopic chest piece is to keep its internal volume at a minimum and have it so shaped that in the case of an obese patient or one with an inelastic chest wall the bell will not fill with flesh to such an extent as to decrease effectively the diameter of the enclosed diaphragm.

15 The diaphragm type of chest piece (Bowles type) which is commonly used in auscultation is especially useful in detecting faint high pitched sounds. When it is applied to a patient's chest the principle of operation of the Bowles chest piece is similar to that of the open bell except that additional attenuation of the lower pitched heart and chest sound components is obtainable with the Bowles chest piece and thus prevents masking of the higher pitched components.

16 In the Bowles chest piece as in the open type of chest piece the air volume should be made as small as possible in order to obtain maximum efficiency.

17 Between 60 and 400 cycles per second which includes most of the auscultatory region tests show that the binaural method of auscultation through rubber tubes is on an average 20 decibels better than the monaural method with the ear directly applied to the stethoscope. A 20 decibel difference is equivalent to a tenfold increase in sound pressure at the ear drum. Only between 850 and 1000 cycles per second is monaural or direct auscultation more efficient than binaural and this range is too high to be practically useful.

18 The changes in the efficiency of an acoustic stethoscope which are caused by varying the length of the tubing although they are not given any consideration by stethoscope users produce an effect upon the quality of sounds. Tests show that below 100 cycles per second the efficiency is not materially affected by tubing length. Between 100 and 1000 cycles per second tubing length exerts a considerable effect that is the efficiency decreases with increased tubing length. This efficiency loss occurs in the region of the low intensity high pitched diastolic murmurs and every possible increase in efficiency in this region is of utmost value.

19 In order to obtain the most efficient tubing dimensions one should make the tubing as short as possible and compromise on the resistance and volume components. The compromise may be approached by plotting a graph representing efficiency versus volume effect and another representing efficiency versus friction.

tional resistance effect where the two curves intersect is the point of optimum efficiency

20 For general clinical use an electrical amplifying stethoscope must transmit sounds to the observer with a quality and fidelity equal to that of the average acoustic stethoscope. A modification of the frequency response characteristic of an electrical stethoscope will definitely alter the quality and character of the sounds.

21 An amplifying stethoscope is not primarily an instrument to be used for making sounds many times louder than they can be heard with an acoustic stethoscope. The major advantage of the amplifying stethoscope over the acoustic stethoscope is that it enables one to adjust the intensity to the desired level and thus eliminate a number of modifying characteristics peculiar to human hearing which cannot be overcome with the acoustic stethoscope.

22 When filters either electrical or acoustic are used with an amplifying stethoscope they should possess frequency response characteristics similar to those of the various open and diaphragm chest pieces.

23 For teaching purposes a loud speaker may be used in conjunction with the amplifying stethoscope. The over all frequency response of the loud speaker and amplifying stethoscope must be identical with that of the average acoustic stethoscope in order not to modify the quality and character of the sounds.

24 In order to maintain an identical and known relationship between sounds heard and as recorded the recording galvanometer and audiophone must be fed from the same source that is the same electrical pulsations which pass to the audiophone are fed into the galvanometer.

The 1942 paper by Rappaport and Sprague was entitled *The Graphic Registration of the Normal Heart Sounds* *Am Heart J* 1942 XXII 591

1 When a patient is auscultated in the usual stethoscopic manner the observer does not hear the cardiac vibrations as they actually exist at the source because of three major forms of modification namely

a The heart sounds are altered in their transmission from the source to the surface of the chest

b The heart sounds that reach the surface of the chest are additionally modified by the acoustic stethoscope and the type of chest piece employed

c The observer does not perceive the heart sound vibrations as they are transmitted to the ears by the acoustic stethoscope

2 The three major forms of cardiac sound modification are related to auscultation as follows

a The chest transmissional factor must be considered and handled as a variable quantity

b Modification effects that are introduced by acoustic stethoscopes and their chest pieces may be made non variable. No attempts at stethoscopic standardization have as yet been made. Until such standardizations are accomplished the stethoscopic factor must be considered as a variable quantity in auscultation

c Modification effects that are introduced by average normal hearing may be considered as a constant quantity in auscultation with the condition that personal factors such as auscultatory experience, fatigue, surrounding noise level and rhythmic concentration ability are omitted

3 The three major forms of cardiac sound modification that are encountered in auscultation may have the following relationships to phonocardiography

a In phonocardiography as in auscultation the chest factor must be considered as a variable quantity

b The modification effects that are introduced by an acoustic stethoscope and its chest pieces in auscultation may be reproduced perfectly by phonocardiography

c The logarithmic type of modification that is introduced in auscultation by average normal hearing may also be reproduced by phonocardiography

4 Phonocardiographic registration may therefore be considered according to the degree of modification introduced namely

a Linear phonocardiography or the registration of the sound vibrations as they exist on the surface of the chest

b Stethoscopic phonocardiography or the registration of the sound vibrations as they are transmitted to the ears by an average acoustic stethoscope

c Logarithmic (human audiographic) phonocardiography or the registration of sound vibrations as they are perceived by a competent observer if the personal factors are omitted

5 Linear stethoscopic and logarithmic phonocardiography are directly related to auscultation. Each phonocardiographic method is a representation of a definite stage of sound transmission in auscultation. Deviations may be introduced by a phonocardiograph with frequency response characteristics other than linear stethoscopic or logarithmic. Such deviations bear no direct relationship to the auscultatory transmission and detection stages. Therefore a phonocardiograph with other than linear stethoscopic or logarithmic characteristics must be considered as either an apparatus of poor design or an expression of the designer's personal opinion unless the deviation is based upon a natural constant.

6 The linear phonocardiograph is essentially an electrical sphygmograph which possesses several advantageous characteristics not common to the segment capsule or direct optical type of sphygmograph.

7 A linear phonocardiogram when registered over the apex is an apex cardiogram or apex beat tracing.

8 A chest piece was devised which makes possible simultaneous phonocardiographic registrations over the same precordial area. For example this dual chest piece is useful for simultaneously registering the apex beat and the stethoscopic or logarithmic phonocardiogram at the apex. Clinically such simultaneous registrations may be useful in differentiating between the third heart sound and the opening snap of the mitral valve when the isometric relaxation phase of the left ventricle is shortened by mitral regurgitation. The apex cardiogram is also useful in timing diastolic events as in venous pulse registration. In some persons it is rather difficult to record the venous pulse in such cases the apex cardiogram may be registered instead.

9 The first heart sound is composed of four components namely

a The first which is caused by residual vibrations of auricular origin

b The second which is produced at the beginning of the isometric contraction phase of the cardiac cycle (closure of the mitral and tricuspid valves)

c The third which is caused by the opening of the semilunar valves

d The fourth which is caused by the acceleration of the blood in the arterial vessels during the maximum ejection phase of ventricular systole

10 The linear phonocardiograph is capable of registering the first and fourth

components of the first heart sound efficiently but is very inefficient in the registration of the second and third components

11 The stethoscopic phonocardiograph registers the first and fourth components of the first heart sound with some attenuation but does not obliterate the vibrations. The second and third components are registered distinctly

"12 The logarithmic phonocardiograph obliterates the first and fourth components of the first heart sound of most normal persons and registers the second and third components distinctly

"13 When a normal person is ausculted the observer rarely hears the first and fourth components of the first heart sound the second and third components are well heard. Logarithmic hearing (as indicated by logarithmic phonocardiography) is responsible for this auscultatory condition because of the greater relative attenuation of the low frequency first and fourth components than of the higher frequency second and third components. Logarithmic attenuation of the first and fourth components is of sufficient magnitude to bring them below the level of human audibility

14 A simultaneous stethoscopic or logarithmic phonocardiogram and venous pulse tracing may serve as a means of differentiating between a prolonged first heart sound and a first heart sound which is followed by a short systolic murmur. In the latter instance it extends beyond the c wave peak

15 Our observations indicate that the second normal heart sound may be composed of four components namely

a The first vibrations which represent the beginning of the diastolic fall in pressure with ventricular relaxation

b The second group of vibrations which are caused by the closure of the semilunar valves (termination of ventricular systole)

c The third group which are most likely due to the arterial wall and blood column vibrations. An additional possible source of vibration in this phase of the second heart sound may be the natural period vibration of the chest wall which may conceivably be set into oscillation by the second component

d The fourth component is caused by the opening of the mitral and tricuspid valves

16 The logarithmic phonocardiogram almost always totally obliterates the first third and fourth components of the second heart sound vibrations whereas the stethoscopic and linear phonocardiogram may show all four components. This indicates that no matter how competent an observer may be he can hear only the second component of the second heart sound of a normal person because his hearing is logarithmic

17 Although the duration of the normal second heart sound is nearly equal to that of the first, auscultation makes the second sound appear shorter. This is explained by the fact that normally two components are audible in the first heart sound whereas only one is audible in the second heart sound

"21 For maximum accuracy in all types of phonocardiographic analysis a phonocardiograph capable of registering the heart sounds linearly stethoscopically and logarithmically should be employed

Thus it becomes evident that much of the discussion about phonocardiography in the clinic in the past has been unsound because of the failure to



recognize the important differences between the various types of phonocardiograms mentioned above namely the linear the stethoscopic and the logarithmic which not infrequently have been erroneously compared as if they were the same in detail. Despite the importance of their distinction it is possible that many of the vibrations that are inaudible but that can be recorded may in their variations eventually prove to have almost as much clinical significance as the heart sounds and murmurs themselves this is for future studies to determine. Figure 12 illustrates two of the three types of phonocardiogram—stethoscopic and logarithmic—in the same case (see below)

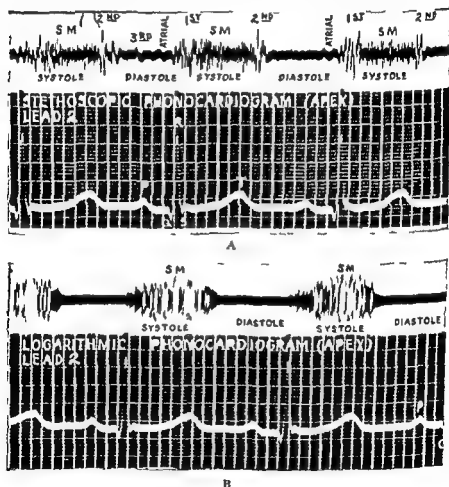


FIG 12 Comparison of stethoscopic and logarithmic phonocardiograms (A and B respectively) taken at the cardiac apex in the same individual with loud systolic murmur. It is of interest to note in the stethoscopic phonocardiogram the third and the atrial sounds which are not audible to the human ear and are not shown in the logarithmic phonocardiogram also the difference in the records of the murmur is quite obvious (kindness of Mr M A Rappaport Sanborn Company Cambridge)

## HEART SOUNDS

There are normally three heart sounds but the third is often very faint or even inaudible. The first sound loudest at the apex is produced by closure of the mitral and tricuspid valves plus an element of muscular contraction and roughly marks the beginning of systole at its very beginning and merged with it is a very short presystolic phase due to atrial contraction which audible or not is indistinguishable from the first sound itself unless there is abnormal lengthening of the interval between the atrial and ventricular contractions. The second sound usually loudest at the base in the pulmonary valve area in children and young adults and in the aortic valve area in the middle aged and elderly is produced by closure of the aortic and pulmonary valves roughly marking the beginning of diastole. The third sound in the normal subject heard as a rule best at the apex and thence halfway to the left sternal border when it is audible at all is probably the result of the vibration of the ventricular walls and atrioventricular valve cusps caused by the inrush of blood in every diastole it is best heard in children after exercise and in the recumbent position. It occurs early in diastole about 0.1 second after the second sound. The opening snap of the atrioventricular (chiefly the mitral) valves if heard at all forms but a late part of the second sound or at most reduplicates it it comes definitely earlier than the time of the third heart sound.

The heart sounds are proportionately increased in intensity when the chest wall is thin and as the result of increase in blood flow by exercise excitement or certain drugs. They are proportionately decreased by a thick chest wall pulmonary emphysema and a state of weakness prostration or shock.

**First heart sound** The first sound is *accentuated* at the apex when the heart action is forceful and the blood flow is rapid as normally after exercise or excitement and abnormally in thyrotoxicosis and in some cases of neurocirculatory asthenia it is most accentuated in the presence of mitral stenosis with forceful heart action. It is not primarily accentuated at the base but it may be so at the lower end of the sternum in very rare cases of tricuspid stenosis.

The first sound is *diminished* at the apex and secondarily at the base in the presence of great myocardial weakness and failure and temporarily when there is a state of vasomotor shock approaching then the usually lesser intensity of the second sound at the apex it gives rise to tic tac rhythm. Extreme weakness of the first heart sound is a bad sign.

The first sound may be *masked* by a systolic murmur either at apex or base. The most complete obliteration of this sort is by the harsh systolic murmur of aortic stenosis.

The first sound at the apex may be delayed by the hemodynamic conditions that exist in mitral stenosis occurring a perceptible interval after the beginning of the apex impulse itself (Cossio 1943).

Finally the first sound may be *reduplicated* such reduplication is best heard

at the apex and results from either (1) an asynchronism of the closures of the mitral and tricuspid valves, due to asynchronism of left and right ventricular contractions as in bundle branch block or to other cause of change in the intraventricular and intra atrial pressure relations or (2) a delay in atrio-ventricular conduction (first grade of heart block) whereby the atrial contraction sound precedes the first ventricular sound by a small fraction of a second

**Second heart sound** The second sound is not primarily accentuated or diminished at the apex. Its *accentuation* at the aortic valve area with the subject at rest is commonest in cases of systemic hypertension especially *hyperpiesia* but it is occasionally louder than normal and metallic in character when there is dilatation of the aorta in syphilitic aortitis and with marked arteriosclerosis. Accentuation of the second sound in the pulmonary valve area may be normally produced by exercise and by deep expiration particularly if the subject is supine. If it is accentuated with the subject at rest and breathing quietly it is a sign of pulmonary hypertension due most commonly to weakness and failure of the left ventricle occasionally to mitral stenosis and rarely to acute or chronic obstruction in the pulmonary circulation itself (as in the acute and chronic cor pulmonale—see Chapter 20) or to congenital defects especially an atrial septal defect. A point of great importance is the relationship between the intensity of the aortic and pulmonary second sounds. In an older person and in a patient with systemic hypertension without heart failure the aortic second sound is greater than the pulmonary second sound. When in such individuals the sounds become equal in intensity or the pulmonary second sound becomes the louder we have evidence of pulmonary hypertension. This in the case of systemic hypertension means weakness and failure of the left ventricle. Recovery from the heart failure is attended by a return of the intensity of the pulmonary second sound to a level below that of the aortic second sound.

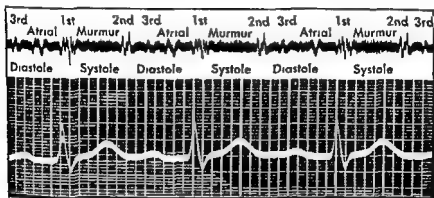
The second sound is primarily *decreased in intensity* to an important degree chiefly at the aortic valve area. This is found particularly with aortic stenosis when the sound may be entirely absent and temporarily with a state of vasomotor shock. With congenital pulmonary valve stenosis the pulmonary second sound may be much diminished or rarely absent. It is to be observed however that the second sound heard at either aortic or pulmonary valve area may be transmitted to that point from the other side of the sternum. This fact has been inadequately recognized and noted.

The second sound may be *masked* by a loud early diastolic murmur at the aortic valve area and along the left border of the sternum in occasional cases of marked aortic regurgitation.

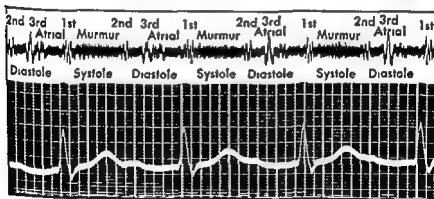
*Reduplication* of the second heart sound is maximal at the base and is due to asynchronous closure of the aortic and pulmonary valves as the result of a disturbed balance of blood pressure relations between the ventricular cavities on the one hand and the aorta and pulmonary artery on the other hand or of asynchronous contraction of the ventricles as in bundle branch block. Re

duplication of the pulmonary second sound is quite common and like the pulmonary systolic murmur may be produced in the normal individual by deep expiration in the supine position. When well marked with the subject at rest it is like accentuation of the pulmonary second sound suggestive of mitral stenosis. The opening snap of the mitral valve if accentuated may reduplicate the second sound at the cardiac apex.

**Third heart sound.** Accentuation of the third sound or the appearance of an extra sound early in diastole (Figure 13) may be caused in slight degree by



A



B

FIG 13 Stethoscopic phonocardiograms showing in A with normal PR interval normal occurrence of first second third and atrial sounds (and a systolic murmur) and in B with prolongation of the PR interval in the same case the superimposition of third and atrial sounds to give a summation effect (kindness of Mr M. A. Rappa port, Sanborn Company Cambridge)

exercise when marked it is the result of one of three underlying causes (1) most commonly dilatation of either ventricle (2) mitral stenosis or (3) delay in atrioventricular conduction so that the atrial contraction sound falls with it to reinforce it. When the third or extra diastolic sound is loud there

is usually a palpable or even visible extra cardiac impulse accompanying it.

Infrequently one hears an extra sound in systole a snap or twang shortly after the first sound and heard best at the cardiac apex. It is a curiosity of academic interest only being found as a rule in healthy individuals without heart disease three cases showing this anomaly and diagnosed correctly ante mortem were reported by Huchard (1893) to have had anomalous chordae tendineae that were undoubtedly the cause of the extra sound an instance of interposition of the atrial contraction in the midsystolic phase has also been noted (Hinohara 1941).

**Gallop rhythm** Gallop rhythm is the descriptive term that has been applied to the auscultatory finding of a well heard extra sound whether in systole or diastole when the heart rate is rather fast, that is 100 or more. Its significance is indicated by the factors responsible for the extra sound as outlined above.

Gallop rhythm is often hard to time but usually it is easy to distinguish between the systolic and diastolic varieties. The former is rare the latter is common. In turn diastolic gallop rhythm is divided when possible into protodiastolic and presystolic in timing but often it is impossible even with graphic records in the presence of considerable tachycardia to decide which is which and one has then to be content with the simple designation "diastolic".

**Protodiastolic gallop rhythm** that is the kind with the loud third sound early in diastole if it can be so timed when located at the cardiac apex is usually a serious sign since left ventricular dilatation is the commonest accompaniment of marked accentuation of the third sound. A protodiastolic gallop rhythm may be heard best at or be limited to the precordium just to the left of the mid or lower sternum in such cases great right ventricular strain is usually very evident and the gallop is probably the result of dilatation of the right ventricle.

A **presystolic gallop** is less serious than a protodiastolic gallop it is found when there is slight delay in atrioventricular conduction or in certain cases with very forceful atrial contraction (in chronic hypertension for example).

A **systolic gallop** is of no clinical importance although it may be present in heart disease.

In rare cases four heart sounds are heard with each heart cycle the first second, and third sounds and a presystolic sound (produced by atrial systole).

**Atrial sounds** Atrial contraction when forceful produces a sound or even a double sound which ordinarily forms a part of and is buried in the regular first sound of the heart when there is delayed conduction or high grade heart block the atrial sound may be faintly audible at the left border of the sternum or at the apex best heard with the bell and with the subject supine (Figure 14).

There are two other points of special interest about heart sounds that deserve mention. One of the curious phenomena in medical observation doubtless dating back to the earliest days of mankind many centuries before auscultation either mediate or immediate is the occasional audibility of the

heartbeat at a distance sometimes with the ear but a few inches from the chest wall and sometimes across a wide room. One cause of such audibility is left pneumothorax another is pneumopericardium and a third is intracardiac and apparently due to rupture of valve cusp chorda or lax infarcted papillary muscle which allows the mitral valve to slap shut with great suddenness. Change of body position and of breathing may greatly affect the degree of audibility.

The other point concerns the variation in time interval that may occur even

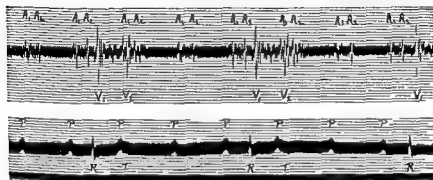


FIG 14 Phonocardiogram (upper tracing) showing double atrial sounds in complete heart block. Electrocardiogram taken simultaneously is shown below. Time interval =  $1/30$  second (Lewy's *Lectures on the Heart* Kindness of Paul B Hoeber Inc New York)

in successive beats between the electric and acoustic records of the heart's action as has been pointed out in two cases of atrial fibrillation (Luisada 1941) the interval was longer after a short diastole.

### VASCULAR SOUNDS

In the great vessels at the base of the heart and extending into the neck and below the clavicles sounds may be heard which are transmitted from the heart. Over the jugular veins especially over the right sided jugular bulb three sounds may be faintly heard if the pulsation there is vigorous and atrial contraction active. These three sounds coincide with the three chief waves normally seen in the jugular pulse the so called *a*, *c* and *v* waves. The first is due to atrial contraction and the other two sounds are undoubtedly the result of transmission of the usual first and second sounds from the heart. Otherwise the only vascular sound (not murmur) that is audible is that found over any large artery when it is compressed. Under certain conditions no compression is needed to hear this arterial sound occurring with the pulse and due to the sudden tension of the arterial wall these conditions are aortic regurgitation and marked peripheral vasodilatation with vigorous heart action both of these conditions being responsible for the relative emptiness of the arteries at the end of diastole when the next pulse comes through. Under such

conditions with compression (or even without it) the sound heard over the greater arteries as over the femoral artery at the groin may be very sharp and has been called the *arterial pistol shot sound*

Finally mention may be made of *fetal heart sounds* which undoubtedly were heard with the ear applied to the abdominal wall long before stethoscopes were invented. They are usually faint and so rapid that it may be difficult to distinguish between the first and second heart sounds. They are generally well heard with the bell receiver attached to the binaural stethoscope. Disturbances of rhythm and rate of temporary significance may be noted and rarely murmurs or arrhythmia of permanent importance such as congenital heart block may be found. Little study has as yet been directed to the possibility of diagnosing heart disease from fetal heart sounds although occasional fetal phonocardiograms have been obtained.

### CARDIOVASCULAR MURMURS

Cardiovascular murmurs like thrills are produced by the vibration of the valves and walls of the heart and great vessels resulting from the rush of blood from a passage of relatively narrow caliber to one of much greater caliber, and by the vibration of a torn or everted valve cusp or of some tissue floating in the blood stream one end of which tissue is fixed to valve or to heart or vessel wall and quite likely by the effect of certain forceful eddies of the blood in its course through the heart. Considering the sinuous course of the blood stream it is surprising that murmurs are not routinely found over all hearts whether normal or not rather than that they occur in only a certain number under basal conditions.

Speed of blood flow is the most important modifying factor. If the flow is fast the murmur will be louder. If the flow is slow the murmur will become fainter and if the flow is very slow the murmur may disappear altogether. External modifying factors as in the case of heart sounds are common. These include obesity and emphysema which diminish the loudness of the murmurs and leanness which increases their loudness. In children murmurs are more easily heard than in adults. The transmission of murmurs in direction and extent depends partly on the loudness of the murmur partly on muscular and bony conduction in contrast to the damping action of air fluid and fat and partly on the direction of flow of the responsible blood stream.

Certain other observations about murmurs are of importance before discussing the individual types. Narrowing of a stream of blood without a fairly abrupt dilatation of the caliber of the containing vessel or chamber further on does not cause murmurs. Roughening of the surface of the walls of heart or blood vessels does not cause murmurs unless there are appreciable projections or torn fragments to vibrate in the blood stream. It is the relation between the calibers of two adjoining parts of the heart or blood vessels and not the absolute size of the caliber of either that determines the production of murmurs. For example there may be a loud systolic murmur in the second inter

costal space close to the sternum if the aorta is dilated even though the aortic valve is normal just as there may be if the aortic valve is stenosed and the aorta of normal caliber. Also even though the mitral valve is normal there may be an apical diastolic rumble if well marked dilatation of the left ventricular cavity (with or without aortic regurgitation) is present just as there may be if the mitral valve is stenosed and the left ventricular chamber is of normal size. The combination of the two factors in either case that is valvular stenosis and dilatation of aorta or of left ventricular cavity favors an increase in the murmur which may be caused by either factor alone.

Heart murmurs may be temporary and due to relatively unimportant functional disturbances. It is of great importance to recognize and remember that most systolic murmurs do not indicate the presence of any structural or organic heart disease. Nevertheless serious diagnoses and bad prognoses have frequently been made largely on the basis of such murmurs. On the other hand it should be recognized that even slight systolic murmurs except in the pulmonary valve area may be abnormal they demand study as to their cause. Often they are found to be unimportant functional murmurs but frequently they are evidence of the presence of some important or serious disease acting on the circulatory apparatus even though there be no heart disease itself. These facts require the application of study and common sense to the interpretation of murmurs and avoidance of the extreme views with overemphasis and underemphasis which have held sway during the swing of the pendulum in the past generation.

At this point I would like to urge a revision of the nomenclature of heart murmurs following suggestions published by Adams Craib and myself (1942). The old time worn phrases functional and organic as applied to murmurs are highly unsatisfactory for important reasons in each case. Functional has been used equally to signify physiologic and pathologic and even when its interpretation is the latter there is no separation as to extracardiac or intracardiac causation. Organic has been in the past limited to structural deformity of a valve even though there may be present much more serious organic disease of the heart than valvular deformity to cause a murmur which has been labeled functional. Also it is often impossible to decide at first at least whether valvular deformity or cardiac dilatation without valvular disease is responsible for a murmur even though it is obviously pathologic. Therefore we recommend that the terms functional and organic as applied to murmurs be dropped and the designations physiologic and pathologic used instead with proper subdivision of the latter into extracardiac causation as from anemia and intracardiac causation as from myocardial involvement (rheumatic myocarditis myocardial infarction or myocardial failure) on the one hand and valvular deformity (with stenosis regurgitation or both) on the other. There may of course be multiple causes for pathologic murmurs in the same case. And in those cases in which we cannot tell whether a murmur is physiologic or pathologic we should so indicate.

Furthermore it is of great importance to realize that serious heart disease



(or other diseases) may be present in the absence of all heart murmurs, and even with normal heart sounds in some cases. Hypertensive heart disease, congenital heart disease, the thyroid heart, syphilitic aortitis, and serious coronary disease with or without angina pectoris may be unattended by heart murmurs. Moreover, some conditions while slight in extent give rise to marked murmurs, and when greater in degree they become murmurless. This may be illustrated by three instances. If mitral regurgitation, functional or organic, is slight in degree with forceful heart action, there is likely to be a loud apical systolic murmur due to the small aperture; if this mitral regurgitation becomes very extensive with a very large aperture between ventricle and atrium, no murmur at all may be found, even though the condition is much worse. If a congenital defect of the ventricular septum is small, as is the rule, a loud systolic murmur with thrill characteristic of the condition results; but if the defect is so extreme that the septum is wholly lacking or only rudimentary, there is no resultant murmur at all, while the defect is of course far more serious. These facts are easily explained by the first comments made above about murmurs. A third example is in the case of stenosis of aortic or mitral valve with well marked murmur; when heart failure of serious degree sets in, this murmur decreases in intensity and may even disappear; in rare cases, moreover, the presystolic phase of the mitral diastolic murmur disappears when atrial fibrillation replaces normal rhythm.

The intensity of heart murmurs may be very simply and adequately expressed by gradation as follows: very slight, slight, moderate, loud, and very loud. This classification may be expressed by the terms *grade 1*, *grade 2*, *grade 3*, *grade 4*, and *grade 5*, a very useful procedure as advised by Levine (1933). In addition to notation of the intensity of heart murmurs, there should always be a statement as to their exact timing, character (blowing, rumbling, low or high pitched, etc.), location, and transmission. The terms "constant" and "inconstant" have no value as applied to heart murmurs to distinguish between pathologic and physiologic types, since some of the former are inconstant and many of the latter are constant.

As is the case with heart sounds, so on rare occasions very intense heart murmurs may be heard without a stethoscope and with the ear at some distance from the chest wall, even the width of a room. Such murmurs, either systolic or diastolic in time, are in the main very loud and high pitched and are due to unusual valve deformities, especially rupture of cusps or chordae tendineae.

Finally, it is to be noted that all murmurs heard over the heart are not intracardiac in origin; some are due to the movement of air in the lungs as the mechanical result of cardiac contraction or to the rubbing together of pleural or of pericardial surfaces, even though uninflamed.

**Systolic murmurs.** 1. *At the cardiac apex* (Figure 12, page 80). The systolic murmur heard at the apex of the heart is commonly blowing, beginning with or immediately following the first sound, and varying from very short in length and slight in intensity so that it is just recognizable as a murmur rather than as an impure

or slurred first sound to a very long and loud murmur filling all of systole. The louder this murmur the wider is the area over which it may be heard. Transmission of this murmur to a distance is largely based on the two factors of loudness of murmur and nearness of heart to stethoscope as is true in the case of most murmurs. An apical systolic murmur therefore which is transmitted to the left axilla toward the base of the heart or back of the chest is in the main a loud murmur. This type of apical systolic murmur is due to systolic regurgitation of blood through the mitral valve from ventricle into atrium. This regurgitation may be the result of organic disease (deformity) of the mitral valve usually rheumatic in origin but this is the rarest of the three usual causes. It is more commonly due to organic disease of the heart with dilatation without any deformity of the mitral valve. But it is most commonly due to some condition elsewhere in the body which acts by causing a temporary or permanent dilatation of the heart without any real organic cardiac disease or mitral valve deformity such a condition may be either physiologic (if temporary) as after exercise in a rapidly growing child or pathologic as in severe anemia. When cardiac dilatation is the cause of the mitral regurgitation and murmur there are two factors to blame the relative importance of which it is difficult to judge. The ring of attachment of the mitral valve may be stretched so that the valve no longer fits tightly or the ventricular dilatation by displacing the papillary muscles downward and outward may prevent the chordae tendineae from stretching sufficiently to allow the valve cusps wholly to close. Furthermore it is conceivable that some valves which are originally less perfectly constructed leak with very little provocation. In the case of a deformed mitral valve it is the shortening and fusion of the chordae tendineae due to inflammation and cicatrization as well as the defects of the cusps themselves that allow the regurgitation of the blood stream.

It is not rare for more than one of the three conditions named above causing mitral regurgitation to be present in the same case as for example coronary heart disease with cardiac weakness and dilatation aggravated by severe anemia.

Another known cause for an apical systolic murmur besides mitral regurgitation is transmission of a systolic murmur from the base or from under the lower sternal region such as occurs commonly in cases of aortic stenosis or dilatation and rarely in cases of interventricular septal defect or pulmonary stenosis. Such a transmitted murmur heard at the apex but maximal elsewhere is far rarer than a systolic murmur maximal and originating at or near the apex. Uncommonly the harsh systolic murmur of aortic stenosis is better heard at the apex than at the aortic valve area itself. A point of much value clinically in distinguishing between the systolic murmurs of mitral regurgitation and of aortic stenosis but relatively slightly known or emphasized is that a loud apical systolic murmur due to mitral regurgitation is well heard in the lung bases in the back but poorly at the base of the heart or in the neck while the aortic systolic murmur is poorly heard over the lung bases and well in the neck and at the cardiac apex.

Finally a systolic murmur at the apex is in a few cases obviously due to the movement of air in and out of adjacent or overlying lung tissue caused by the mechanical action of the heartbeat itself or to pericardial or pleural rubbing. Cardiac systole may compress lung tissue especially if it is fixed over the heart at the apex and squeeze air out or it may cause a suction of air into lung tissue which had been compressed by the heart in diastole. It is generally but perhaps not always possible to differentiate this so called respiratory systolic murmur from systolic murmurs of intracardiac origin the respiratory character and particularly its variations in different positions of the body and in different phases of respiration (in one of which especially full inspiration it may disappear entirely) and the relative constancy and quality of the intracardiac murmur usually distinguish between the two. Sometimes rales also are produced in the lungs by the action of the heart causing movement of air back and forth through moisture in the bronchioles this association of rale production with heart action may help to explain respiratory murmurs present in the same case. The most common form of cogwheel respiration is respiration punctuated by frequent respiratory murmurs due to the heart's contraction.

It has been shown that the rubbing together of uninflamed pericardial or pleural surfaces can produce murmurs mostly systolic but sometimes diastolic (Ortiz 1933). Almost certainly some of the extracardiac murmurs heard clinically are of this origin.

There may be other causes for the apical systolic murmur which we do not yet know but certain old terms like hemic and accidental should be omitted. Anemia malnutrition and infections act by causing cardiac dilatation and speeding up the blood flow and so produce pathologic murmurs of extracardiac origin.

The time intensity and character of an apical systolic murmur and even the presence of a palpable thrill do not show whether or not the valve is damaged though the loudest murmurs masking the first sound and accompanied by thrills are more often found with valvular disease than without it. When chronic rheumatic heart disease is present with mitral stenosis the mitral valve lesion may be considered chiefly responsible for the regurgitant murmur and sometimes in young children with a history of recovery from rheumatic fever mitral valve disease may be considered responsible for constant loud apical systolic murmurs even before mitral diastolic murmurs have developed. However it is very important to note that during the acute or subacute rheumatic infection without previous rheumatic attacks both systolic and diastolic murmurs originating at the mitral valve are the result of left ventricular dilatation secondary to the myocardial involvement and not to mitral valve deformity which takes in all probability at least a year and more likely two or three to become established sufficiently to cause murmurs (see Chapters 14 and 26).

A word should be added about the time of the apical systolic murmur. As a rule the murmur begins early in systole and continues much of the way through if it fills systole it is sometimes called holosystolic. The louder and

harsher the murmur the more likely it is to mask not really to replace the first sound. In a few cases it begins at an appreciable interval after the first sound or even in mid or in late systole such a late murmur is more likely to be of respiratory than of intracardiac origin but it may be due to the slow yielding in systole of a weak mitral valve ring.

2 *At the base* As in the case of heart sounds there is a distinction between systolic murmurs heard in the second intercostal space just to the right of the sternum and in the same space just to the left of the sternum. For the sake of convenience these regions have been called the aortic and pulmonary valve areas respectively and they will be so considered here.

(a) *Aortic area* There are four chief causes for systolic murmurs heard at the aortic area. They are (1) dilatation of the aorta without aneurysm (2) aortic and subaortic stenosis (3) aortic aneurysm (4) transmission of a systolic murmur from pulmonary area from mid or lower sternum or even from the apex. The commonest cause of an aortic systolic murmur is simple dilatation of the aorta whether due to chronic hypertension the dynamic effect of aortic regurgitation arteriosclerosis or syphilitic aortitis. Upward pressure on heart and great vessels by high diaphragm as in extreme obesity favors the production of an aortic murmur in such cases hypertension is also frequently present. A very important and not infrequent cause of an aortic systolic murmur is aortic stenosis which is most commonly of rheumatic or unknown origin rarely due to congenital subaortic or aortic ring stenosis and in more than slight degree only occasionally the result primarily of calcareous disease although calcification is often superimposed on an already damaged aortic valve to increase the degree of its stenosis in the more chronic cases. In the case of congenital subaortic stenosis that is of stenosis of the infundibulum or outflow tract of the left ventricle the loud rough systolic murmur may be better heard in the third right intercostal space or even over the sternum itself than in the second space. A murmur transmitted to the aortic area from elsewhere is not rare. One of the least common causes of an aortic systolic murmur is a sacular aneurysm usually of the ascending aorta or a dissecting aneurysm of the thoracic aorta.

The aortic systolic murmur is generally blowing in character except in aortic stenosis when it is harsh and rough. It varies in intensity from slight to very loud the latter intensity usually indicating aortic stenosis in which condition the murmur may be so intense that it is heard all over the chest neck and head and even in rare cases with the naked ear a few inches from the chest wall. The aortic systolic murmur tends to be transmitted often in its fullest intensity to the cardiac apex itself along the larger arteries and bones into the neck shoulders arms and back (especially down the spine) and even along the abdominal aorta the louder it is the further it is transmitted. With a very loud murmur there is usually a palpable thrill most marked when the murmur is especially rough as is often the case with aortic stenosis. The time of onset of the murmur is almost invariably very early and if the murmur is loud and harsh it commonly masks the first sound completely. The duration

of the murmur is somewhat variable but usually extends throughout systole and in the case of aortic stenosis it is frequently followed by no second sound at all

(b) *Pulmonary area* A systolic murmur at the pulmonary valve area is often found. It is the commonest of all heart murmurs and if it is absent with the subject in the upright position it can usually be brought out in the normal individual as well as in the cardiac patient by the assumption of the supine position especially in full expiration. Therefore the pulmonary systolic murmur may be considered to be a normal physiologic event unless of considerable intensity in the upright position even then it should be analyzed carefully before being called abnormal. The mechanism of this physiologic murmur is not known but it is probably associated with a dilatation of the pulmonary artery under increased pulmonary pressure as in full expiration (or best in the Valsalva experiment which is an attempted forced expiration with the glottis closed) or with a kinking of the artery by change in position or with other factors which may lead to dilatation. This physiologic pulmonary systolic murmur is blowing in character begins early in systole but does not mask the first sound extends through most of systole is as a rule not widely transmitted and is associated frequently with accentuation or reduplication of the pulmonary second sound physiologically produced in a similar way.

Pathologic dilatation of the pulmonary artery is a much less common but far more important cause of a blowing pulmonary systolic murmur (of varying intensity) than is temporary physiologic dilatation. The causes of this pathologic dilatation are (1) pulmonary hypertension most commonly due to failure of the left ventricle but also to mitral stenosis and certain congenital anomalies; serious chronic pulmonary fibrosis and emphysema and the rare pulmonary endarteritis (2) thyrotoxicosis which greatly increases the pulmonary blood flow and so dilates the pulmonary artery and (3) rare congenital defects especially an atrial septal defect with resultant flooding of the pulmonary circulation (see Chapter 13). Here as in the case of the physiologic increase of pressure in the pulmonary circulation the pulmonary second sound is often markedly accentuated and may in rare cases be followed by a blowing diastolic murmur which is discussed later in this chapter.

Other causes of a pulmonary systolic murmur are rather rare though important. Congenital pulmonary stenosis is as a rule but not always accompanied by a loud harsh systolic murmur usually masking the first sound and by a palpable thrill. Both murmur and thrill are maximal in the second left interspace near the sternum sometimes a little higher (second rib) and sometimes if the infundibulum of the right ventricle and not the pulmonary valve is stenosed a little lower (third rib or third interspace). Such a difference in site of the maximal murmur and thrill may not however mean a difference in pathologic state. The character, time relations and intensity of the murmur resemble those of aortic stenosis but the positions differ and the pulmonary stenosis murmur is not so widely transmitted it is sometimes localized to a small area only 2 or 3 cm in diameter but it is usually very well

heard in the lung bases behind Patency of the ductus arteriosus particularly in infants may cause a moderate blowing pulmonary systolic murmur, not so intense as that of pulmonary stenosis and alone not to be interpreted as evidence of such patency A patent ductus arteriosus can be diagnosed by auscultation however only if there is a continuous humming top murmur Aneurysm of the aortic arch or descending aorta may cause rarely a systolic murmur in the pulmonary area as may also the occasional congenital coarctation of the aorta if well marked and the extremely rare true aneurysms of the pulmonary artery itself Finally systolic murmurs from other regions especially from the aortic area may be transmitted to the pulmonary area The fact that the very loud systolic murmurs and pronounced systolic thrills of both aortic stenosis and pulmonary stenosis are sometimes perceived almost equally well on both sides of the sternum or even best over the sternum itself makes the differentiation of these two conditions by auscultation alone at times difficult or even impossible the best differentiation by auscultation is by the transmission of the murmurs that of aortic stenosis being *widely and loudly* transmitted except to the lung bases where it is heard only faintly, and that of pulmonary stenosis being transmitted *not far* except to the lung bases

3 *Elsewhere over the precordium* There are two other areas besides apex and aortic and pulmonary areas where auscultation may reveal maximal sites for systolic murmurs They are at the lower end of the sternum and in the third and fourth intercostal spaces just to the left of the sternum Ruling out in the first place systolic murmurs transmitted from other areas where they are generally much louder we come to the very rare systolic murmurs originating in these two regions To the left of the sternum in the third or fourth intercostal space or in both a loud blowing systolic murmur may be heard in cases of congenital interventricular septal defect If such defect is uncomplicated (as is sometimes not the case) such a murmur is called the Roger murmur (and the condition Roger's disease) A palpable thrill usually accompanies this murmur Pulmonary or more probably infundibular stenosis is a less likely congenital cause for this type and position of murmur Finally a systolic murmur originating under the lower end of the sternum is rare signifying tricuspid regurgitation with a considerable degree of tricuspid stenosis Tricuspid regurgitation which is most often due to dilatation and not to valve damage is in contrast to mitral regurgitation rarely accompanied by murmurs probably because the tricuspid ring is larger and the right heart chamber pressure differences less Mitral regurgitation aortic stenosis or some congenital cardiac defect is by transmission much more likely than is tricuspid disease to cause a loud systolic murmur at the lower end of the sternum

4 *Vascular systolic murmurs* Murmurs systolic in time that are coincident with the appearance of the pulse wave are common over arteries At the base of the heart and in the main branches of the aorta three causes exist for their occurrence marked arterial dilatation with or without sacular aneurysms constriction by internal deformity or pressure from without (with the murmur

found at the end of the constriction where the caliber increases again to normal or beyond) and transmission of a loud murmur from the aortic area as in aortic stenosis. Over the larger peripheral arteries like the brachial, femoral, and popliteal pressure applied artificially from without easily produces systolic murmurs and thrills as is observed routinely in blood pressure studies. Also compression by tumors, cicatrices or other causes may give rise to systolic murmurs and thrills as may large aneurysms with active blood flow. Over the veins isolated systolic murmurs are not found but as will later be mentioned continuous murmurs may be present. Over the thyroid gland in exophthalmic goiter a very striking vascular murmur is heard called a bruit generally continuous with systolic accentuation and accompanied by a palpable thrill; it is doubtless due to the greatly increased arteriovenous blood flow through the hyperactive gland.

Systolic murmurs may be heard rather easily with either bell or Bowl type of stethoscopic chest piece but as they rise in pitch they are more readily perceived by the Bowles receiver. Certain murmurs are better brought out and are more likely to appear with the subject in one position than in another as for example the pulmonary systolic murmur which may be produced by the assumption of the supine position. Finally one systolic murmur may be superimposed on another the harsher or louder one predominating making it very difficult to distinguish the two components.

**Diastolic murmurs.** Diastolic murmurs are less common but usually more important than systolic murmurs. They have often been called the most serious auscultatory findings but this is not always so since the careful study of heart sounds and the detection and correct interpretation of certain frequent but neglected systolic murmurs may give us more information about the heart in the long run. Diastolic murmurs are often difficult to hear. It is for their detection that the use of the two stethoscopic chest pieces is so helpful and the examination of the subject in both upright and recumbent positions so important. To test the effect of change in position it is most convenient and generally sufficient to examine the patient first upright and then supine or in the left lateral position. Before proceeding with the special diastolic murmurs of intracardiac origin it should be noted that in diastole as in systole, though far less often, respiratory murmurs may be produced by the action of the heart in squeezing air out of or sucking air into lung tissue especially if the lung happens to be fixed in close contact with the heart. Such murmurs can be distinguished almost always by their respiratory quality by the ease with which they are caused to vary or disappear with forced respiration or change in body position by the fact that they tend to occur at an interval after the second heart sound and not directly with it frequently by their nearness to the ear and sometimes by the simultaneous occurrence of pulmonary rales due to the mechanical effect of the heart's action in sucking air in and out through moisture filled bronchioles. It is quite likely that a few of these so called respiratory or other extracardiac diastolic murmurs are like systolic

murmurs produced by the friction of uninflamed pericardial or pleural surfaces (Ortiz 1933)

1 *At the apex* The only two diastolic murmurs heard at the apex with any degree of frequency are those due to mitral stenosis and to aortic regurgitation

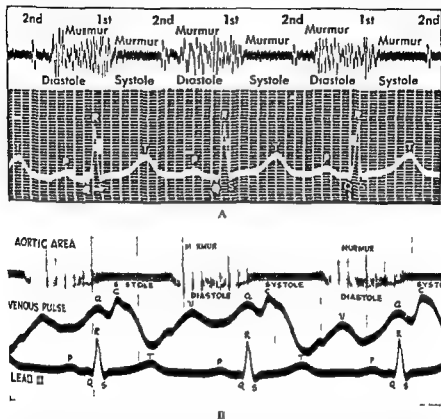


FIG 15 Phonocardiograms showing the diastolic murmurs of mitral stenosis and of aortic regurgitation (A) Stethoscopic electrocardiogram of a classical case of mitral stenosis with very rough mitral diastolic murmur sometimes with presystolic accentuation (note the first beat on the record) Slight systolic murmur also. Observe the interval of relative silence between the second sound and the beginning of the middiastolic murmur of mitral stenosis in comparison with the absence of such an interval in the case of the aortic diastolic murmur in (B) (B) Logarithmic phonocardiogram showing the very musical character of the high pitched aortic diastolic murmur associated with retroversion of an aortic cusp. Note that systole is clear. Simultaneous venous pulse tracing and Lead 2 of the electrocardiogram are recorded (kindness of Mr M A Rappaport Sanborn Company Cambridge)

These murmurs unlike superimposed systolic murmurs are so different that even when they occur together they can be differentiated

(a) *Organic mitral stenosis* The murmur of mitral stenosis (Figure 15A) has usually five characteristics that distinguish it from the murmur of aortic regurgitation (1) a rough rumbling character generally of low pitch and



sometimes so low as to be scarcely audible even to a trained ear (2) a failure to appear with or to follow immediately the second heart sound but instead an onset at a definite interval of time after the second sound that time interval being the ordinary interval between the second and third sounds of the heart (3) a localization at the apex often over a small area of but 2 or 3 cm in diameter with no transmission beyond a characteristic that not infrequently causes the murmur to be missed entirely unless the examination is very careful and complete (4) a better perception by the employment of the bell chest piece of the stethoscope than by the employment of other types whose limited use may fail entirely to pick up the murmur when it is not loud and (5) a better perception with the patient recumbent the upright position sometimes failing to reveal the murmur even with the use of the bell receiver To these five characteristics may be added five others found less regularly but which are very useful in distinguishing the murmur (6) a palpable thrill localized closely as a rule over the apex in diastole usually somewhat shorter than the murmur (7) the presence in normal rhythm of a striking accentuation of the murmur in presystole just before or at the beginning of the first sound of the heart and due to the effect of atrial systole but absent if atrial fibrillation is present if the mitral stenosis is relatively slight or if the atrium is empty or weak when it contracts at the end of a prolonged diastole (8) the usual presence of an accentuated first heart sound at the apex so often characteristic of mitral stenosis (9) the common accentuation of the pulmonary second sound and (10) the frequent presence of a loud third heart sound at the left of the lower end of the sternum or in the space between this area and the apex and probably due to dilatation of the right ventricle

The murmur of mitral stenosis is explained by the vibration of heart walls and valve caused by the rush of blood through the stenosed mitral valve into the left ventricular cavity Its greatest intensity is usually at its onset at the time of the third sound when the flow of blood into the ventricle begins (which flow does not occur immediately at the time of the second sound when the aortic valves close at the end of systole) At the onset of the mitral diastolic murmur the flow of blood is as a rule faster than at other times because the intra atrial pressure with left atrium full of blood is greatest at such a time in relation to the low intraventricular pressure which in turn is caused by the passive elastic diastolic ventricular dilatation The force of the blood stream decreases as diastole proceeds and both murmur and thrill tend to fall off in intensity in diminuendo fashion to die away entirely if diastole is long (with atrium almost empty and ventricle full) or if the degree of the mitral stenosis is but slight If normal rhythm exists there is another increase in the speed of blood flow from atrium to ventricle in presystole due to atrial contraction If on account of a short diastole (fast heart rate) or marked valvular stenosis there is still a good deal of blood left in the atrium and still room for more in the ventricle the increase in blood flow through the stenosed mitral valve may be sufficient to cause a final accentuation variable in degree

and sometimes marked of the diastolic murmur and thrill just before the first sound or to make it audible again if it has entirely disappeared

The presystolic accentuation of the mitral diastolic murmur was formerly described as crescendo in character but the crescendo is actually an auditory illusion as shown by phonocardiograms and careful auscultation the illusion is due to the combined presence of a sudden accentuation of a murmur that has largely died away and the sharp first heart sound that terminates it This presystolic part of the murmur of mitral stenosis was at one time considered to be the whole murmur or at least the earliest to appear or the most important or characteristic part. But now we regard it as simply one part of the whole murmur at times striking to be sure but often absent as for example when there is atrial fibrillation (that is no orderly forceful atrial contraction) or too slight a degree of mitral stenosis to produce it If we would rely solely upon the presence of a presystolic murmur for a diagnosis of mitral stenosis we should miss at least half the cases of this valvular lesion Rarely may a presystolic murmur be present alone without a middiastolic murmur when the force and speed of blood flow through the stenosed valve happen to be greater in presystole than in middiastole and the degree of stenosis not sufficient to cause a murmur at both times Careful study of the case should however be made before recording a diagnosis of mitral stenosis on the basis of what appears to be a presystolic murmur alone without any diastolic rumble or murmur preceding it Marked accentuation and slurring of the first heart sound such as not infrequently occur in an overactive heart may give a semblance of a slight presystolic murmur and cause an erroneous diagnosis of mitral stenosis to be made when excitement exertion some nervous factor as in neurocirculatory asthenia or thyrotoxicosis is responsible If for any reason there is a suspicion of the possible presence of mitral stenosis because of rheumatic history sharp first sound loud third sound or unusual heart shape size or symptoms and no mitral diastolic murmur is present exercise (or the administration of a nitrite) may be used as a test to increase the rate of the heart and the speed of blood flow and to bring out a typical diastolic rumble at the apex Always it is best to examine the subject recumbent after such a test

Rarely the murmur of mitral stenosis may be a gentle and moderately high pitched blow following the third sound but almost invariably it is rumbling in nature and low pitched when the stenosis is pronounced An apical systolic murmur of mitral regurgitation may or may not be associated with the diastolic murmur of mitral stenosis The louder either one of these murmurs the less intense is the other and if either murmur is marked the other usually is absent

Cossio and Berconsky (1943) have pointed out the actual systolic rather than presystolic timing of the very brief vibrations (murmurs) that may precede the delayed and accentuated first heart sounds following the shorter diastolic pauses in atrial fibrillation in cases of mitral stenosis

(b) *Functional mitral stenosis* There is another fairly common cause of the mitral diastolic murmur besides actual organic mitral stenosis this is relative mitral stenosis due to considerable dilatation of the left ventricle with the valve normal or not sufficiently damaged to give rise alone to the obstructive diastolic murmur. The clinical conditions in which such relative mitral stenosis is found are chiefly three namely moderate to severe acute or subacute rheumatic myocarditis high grades of anemia from any cause and well marked aortic regurgitation. In a few scattered cases other causes of left ventricular dilatation are responsible such as congestive heart failure but as a rule cardiac dilatation associated with ordinary congestive failure is not attended by a mitral diastolic murmur in such cases there tends to be a third sound instead. Why this is so is not yet clear but it is probably because the blood flow is not fast enough in these hearts.

In the case of aortic regurgitation various theories have been expressed as to the pathogenesis of the mitral diastolic murmur. It has been generally thought that the blood stream regurgitating through the damaged aortic valve especially if the posterior cusp is involved or through the dilated aortic ostium impinges on the anterior cusp of the mitral valve thus forcing it back and producing a functional stenosis at a time in diastole when the blood stream is pouring from atrium into ventricle another theory suggests the production of the murmur by the contact of the two streams from aortic and mitral valves pouring together into the left ventricle with the anterior cusp of the mitral valve vibrating between them. The best explanation however that fits not only the cases of aortic regurgitation but also the cases showing the characteristic murmur with no valve lesion at all is that the left ventricular dilatation is sufficient in degree to give rise to a murmur when the caliber of the blood stream coming through the normal mitral valve suddenly widens out. The time relations quality location and other characteristics of this diastolic murmur of functional mitral stenosis are exactly the same as for organic mitral stenosis except that there is as a rule less intensity to it and usually no associated palpable thrill. When the mitral diastolic murmur is found with aortic regurgitation without mitral stenosis it has been called the Austin Flint murmur (Flint 1862).

Flint Austin On Cardiac Murmurs *Am J M Sc* 1862 N S XLIV 29

Page 51 As a rule the force of the mitral direct current is not sufficient to develop a murmur unless there be mitral contraction. Is this murmur ever produced without any mitral lesions? One would *a priori* suppose the answer to this question to be in the negative. Clinical observation however shows that the question is to be answered in the affirmative. I have met with two cases in which a well marked mitral direct murmur existed and after death in one of the cases no mitral lesions were found in the other case the lesion was insignificant. I will proceed to give an account of these cases and then endeavor to explain the occurrence of the murmur.

A mitral direct murmur then may exist without mitral contraction and with

out any mitral lesions provided there be aortic lesions involving considerable aortic regurgitation. This murmur by no means accompanies aortic regurgitant lesions as a rule we meet with an aortic regurgitant murmur frequently when not accompanied by the mitral direct murmur. The circumstances which may be required to develop functionally the latter murmur in addition to the murmur of aortic regurgitation remain to be ascertained. *Probably enlargement of the left ventricle is one condition* [Italics mine]

(c) *Transmitted murmurs* Other diastolic murmurs that may be heard at the apex are transmitted from elsewhere. They are due to aortic regurgitation frequently to the very rare pulmonary regurgitation seldom and to tricuspid stenosis probably not at all the murmur in this last named condition not being distinguishable at the apex if it could be heard there from the murmur of mitral stenosis which is almost always much more prominent in such cases.

2 *Diastolic murmurs at the base* In the case of basal diastolic murmurs the differentiation of sites is not so important as in the case of basal systolic murmurs since the two diastolic murmurs found are both heard maximally often in the same place and have the same characteristics. Other data therefore than site and characteristics must generally be employed to differentiate them the most important point is that the murmur of aortic regurgitation is far more common than that of pulmonary regurgitation.

(a) *Aortic regurgitation* (Figure 15B) The auscultatory characteristics that distinguish aortic regurgitation from mitral stenosis and tricuspid stenosis but not from pulmonary regurgitation are (1) a blowing rarely musical quality either high or low pitched often very gentle (2) an onset with or at once after the second heart sound the murmur if intense completely masking the sound (3) a maximal audibility over the midsternum and immediately to the left of it in the third and fourth intercostal spaces usually with wide transmission to the apex and left axilla and upward less loudly toward the neck (4) a better perception with the Bowles type of stethoscopic chest piece than with the bell although rarely certain lower pitched aortic diastolic murmurs may be better heard with the bell or even with the naked ear and (5) a better perception as a rule with the patient upright and leaning forward than recumbent. In addition (6) a diastolic thrill is rarely felt accompanying this murmur (7) the murmur continues usually through all or most of diastole decreasing in intensity and never showing a presystolic accentuation (8) the first heart sound is not accentuated in fact frequently both heart sounds are masked by murmurs and (9) an accentuated third heart sound is not usually found. Very often particularly if the diastolic murmur is marked there is also an aortic systolic murmur due either to aortic dilatation or to aortic valve stenosis but in the latter case as in mitral valve disease the louder one murmur becomes the less loud is the other that is the greater the stenosis the less the regurgitation and vice versa. It is common in aortic syphilis with aortic dilatation and regurgitation for both systolic and diastolic murmurs to be loud all over the cardiac area including the second intercostal space just to the right of the sternum with both heart sounds masked by them.

The clinical conditions responsible for the aortic regurgitant diastolic murmur are firstly and much more frequently organic aortic valve disease due to rheumatic infection, syphilitic aortic involvement or sclerotic change and secondly dilatation of the aortic valve ostium without disease of the cusps themselves due occasionally to syphilitic aortitis and rarely to chronic hypertension sclerotic change senile ectasia, dissecting aortic aneurysm or severe anemia. There is a very interesting variation of the aortic diastolic murmur, more commonly found in syphilitic aortitis than in other conditions consisting of a very loud high pitched musical character with thrill and due apparently to eventration of one of the valve cusps (Bellet et al 1939 Nichols, 1940) (see Figure 15B).

Uncommonly the aortic diastolic murmur is heard better in the aortic area that is in the second interspace just to the right of the sternum than it is along the left sternal border whither it generally is transmitted in maximal degree. Such a maximal localization of the murmur in the aortic area is occasionally found in aortic regurgitation associated with marked aortic dilatation due to syphilitic aortitis when the ascending aorta extends further to the right and upward than normally or when along with the aortic valve the ascending aorta is displaced upward and to the right by a very large heart. Also rarely the aortic diastolic murmur is heard better at the cardiac apex or at the lower end of sternum or between these sites than along the left border of the sternum if so it can easily be distinguished from the mitral (or tricuspid) diastolic murmur by its other characteristics described above. Often the diastolic murmurs of aortic regurgitation and of organic or functional mitral stenosis occur together at the apex and can be readily distinguished. Finally it should be stated that the diastolic murmur of aortic regurgitation may be found without any peripheral vascular signs this occurs in the lesser degrees of the valve defect if peripheral vascular signs like the water hammer or capillary pulse are awaited before aortic regurgitation is diagnosed half the cases of this valve lesion will be missed.

(b) *Pulmonary regurgitation* Rare but almost exactly similar in its characteristics to the diastolic murmur of aortic regurgitation in that due to regurgitation through the pulmonary valve. The resemblance may be so nearly complete that a distinction cannot be made by auscultation alone. Rarely however does the pulmonary diastolic murmur ever reach in intensity the loudness frequently found in the case of the aortic diastolic murmur. When it is unusually marked it is louder in the second left interspace (pulmonary valve area) than it is in the third and fourth interspaces and follows a much accentuated pulmonary second sound these are important clues. In cases with well marked pulmonary diastolic murmurs there may also be other tell tale signs namely abnormal visible or palpable pulsation in the pulmonary valve area a loud pulmonary systolic murmur water hammer pulsation in the pulmonary artery and 'dance' of the lung hiluses seen by roentgen ray and abnormal right axis deviation by electrocardiogram. Usually the pulmonary diastolic murmur is not transmitted so widely as is the aortic. With a loud

blowing diastolic murmur along the left sternal border well marked peripheral vascular signs such as the water hammer and capillary pulse are present if the murmur is due to aortic regurgitation and absent if it is due to pulmonary regurgitation this does not apply if the murmur is slight or moderate Percussion and roentgenologic and electrocardiographic studies are especially helpful in the differentiation between aortic and pulmonary regurgitation The clinical conditions underlying pulmonary regurgitation are most commonly (1) mitral stenosis causing increased pressure in the pulmonary circulation and dilatation of the pulmonary artery and valve ring without damage to the valve and rarely the remaining causes (2) chronic failure of the left ventricle with pulmonary vascular congestion and hypertension (3) chronic lung disease giving rise to the same mechanical conditions (4) chronic obliterating pulmonary endarteritis (5) congenital defect of the atrial septum with consequent flooding of the pulmonary circulation (6) congenital defect of the pulmonary valve giving rise to regurgitation (7) perhaps wide patency of the ductus arteriosus and (8) acute or chronic endocarditis of the pulmonary valve itself If mitral stenosis is the underlying clinical cause of the functional pulmonary regurgitation the diastolic murmur resulting is called the Graham Steell murmur (Steell 1881 1888)

Steell Graham *Physical Signs of Cardiac Disease* Edinburgh 1881 2nd ed page 43

Dr Balfour states that a diastolic murmur due to mitral stenosis may be audible and have its maximal intensity in the pulmonary area This murmur is soft and blowing unlike the apex true diastolic murmur of mitral stenosis and is probably produced in the pulmonary artery and infundibulum of the right ventricle as a murmur of high pressure the pulmonary artery being dilated and its valves permitting of a certain amount of regurgitation This murmur is not usually constant at least when first developed (See also *M Chronicle* Manchester December 1888 'The Murmur of High Pressure in the Pulmonary Artery')

3 Elsewhere over the precordium the diastolic murmurs heard are those already described transmitted there except for one very rare murmur heard maximally and often solely over the lower end of the sternum This exception is the diastolic murmur of *tricuspid stenosis* In every characteristic except that of position it is similar to the mitral diastolic murmur but it is usually less intense and may have more of a blowing nature In only extremely rare instances is it heard without an equally loud or louder mitral diastolic murmur and since sometimes the latter murmur is transmitted away from the apex and is heard at the lower end of the sternum a diagnosis of tricuspid stenosis by auscultation is rarely justified It may be suspected if the typical diastolic murmur is louder over the lower end of the sternum than elsewhere over the precordium The presence of a palpable diastolic thrill localized at the same place or much more marked there than at the apex supports the diagnosis of tricuspid stenosis Other signs obtained by roentgen ray and general physical

examination are important. The underlying clinical condition is organic tricuspid stenosis due to chronic rheumatic endocarditis.

Functional tricuspid stenosis had not been described before I encountered several cases which I believed to be such with well localized mid diastolic murmurs near the lower end of the sternum, mitral diastolic murmurs at the apex, and loud pulmonary diastolic murmurs. Autopsy of one of the cases showed mitral stenosis, obstructing thrombi in left atrium and pulmonary vessels, and marked dilatation of pulmonary artery and right ventricle with no organic disease of pulmonary, aortic or tricuspid valves. This I reported in the third edition of this book in 1944 and have confirmed since.

4 *Vascular diastolic murmurs* Vascular diastolic murmurs are rare. Over the great vessels at the base of the heart there may be transmitted for a short distance a diastolic murmur originating in the heart, but this is far less common or marked than in the case of systolic murmurs. Otherwise there is only the diastolic murmur produced in cases of aortic regurgitation or marked peripheral vasodilatation by the application of moderate to marked pressure over the larger arteries (best over femoral or brachial artery). First there appears the pistol shot sound and systolic murmur, and then as the pressure is increased a slight to moderate blowing diastolic murmur is also heard (not a continuous murmur). The appearance of such a murmur is called Duroziez's sign (Duroziez, 1861). The differentiation of the two causes of the murmur has been pointed out by Blumgart and Ernestine (1933) who showed that pressure with the distal and not proximal edge of the auscultatory bell will produce the murmur if aortic regurgitation is the factor responsible, while the reverse is true in cases of peripheral vasodilatation in accord with the direction of blood flow and mechanism of murmur production discussed above.

**Continuous murmurs** There is no continuous murmur of cardiac origin, but there are three of vascular origin and all three of these may be heard over the region of the heart.

1 Probably the most common and certainly the least important cause of such a continuous murmur is the mechanism giving rise to what has been called the *venous hum in the neck* with the subject seated or standing. This murmur of humming character is loudest at the right side of the base of the neck and much less loud on the left side. It is much increased by bending and turning the head to the left, putting the blood vessels on the right side of the neck on the stretch. It is easily and quickly obliterated by light pressure on the neck over the jugular veins sufficient to stop temporarily the downward flow of blood, or by the assumption of the recumbent position—very simple pathognomonic tests. It is a frequent finding in normal individuals, especially children. It is not evidence of any disease or pathologic state. It is probably due to the rapid flow of blood (in the absence of all stasis) through the jugular veins into the jugular bulb and on into the superior vena cava. Its importance so far as the heart is concerned is that it is frequently transmitted downward over the base of the heart, even close to the lower end of the sternum, and may give rise to such erroneous diagnoses as patency of the

ductus arteriosus and even aortic regurgitation if the diastolic phase of the hum happens to be prominent. Such mistakes have been made in the past and since many physicians are unaware that there even exists such a phenomenon it behooves all examiners first to know that it does exist and then to exclude it before making a diagnosis of cardiovascular pathologic conditions. Lian (1937) has also referred to the probability that rapid blood flow in the superior vena cava may be rarely responsible for a continuous murmur heard along the right sternal border.

Brief mention should also be made of the umbilical venous hum heard in some cases of cirrhosis of the liver and in the case of certain congenital venous defects and called the Cruveilhier Baumgarten syndrome (Blain and Clapper 1945).

2 *Patency of the ductus arteriosus* A continuous murmur often with systolic accentuation heard best and sometimes only in the first or second interspace to the left of the sternum a little farther out than the site of the pulmonary systolic murmur and faintly or not at all in the neck is a characteristic sign of patency of the ductus arteriosus. If patency of the ductus complicates congenital dextrocardia or a right aortic arch the continuous murmur is heard at the right border of the upper sternum. This congenital defect may rarely occur however without murmurs or with but a slight to moderate systolic murmur in infancy or when the patent ductus is of very wide caliber. If we can exclude the venous hum in the neck and arteriovenous aneurysms this typical mill wheel humming top machinery or tunnel murmur is pathognomonic of patency of the ductus arteriosus and can usually be confirmed by other findings. The murmur may be transmitted to other parts of the precordium though usually it is not and it may be localized so high in the left side of the chest that it is missed on hasty or careless examination. Its discovery is generally striking and may occasion undue alarm in the mind of an inexperienced examiner. There may or may not be a continuous palpable thrill associated with it there usually is such a thrill if the murmur is intense.

A very interesting new continuous murmur is that produced by the surgical treatment of the tetralogy of Fallot (see Chapter 13) here the subclavian (or innominate) pulmonary artery anastomosis produces a patent ductus like murmur on whichever side of the sternum the procedure is carried out.

3 *Arteriovenous aneurysm* A continuous murmur usually with some accentuation in systole and attended by a thrill is found on auscultation over any direct arteriovenous connection sometimes called an arteriovenous aneurysm wherever it may be whether in the great vessels at the base of the heart (very rare occurrence) in the lungs in the head or neck or in the extremities (the most common site). Its interpretation is generally easy. Such aneurysm is as a rule traumatic in origin by bullet shrapnel knife or even surgical accident (Linton and White 1945) it may be congenital (see Chapter 28).

Appearing abruptly at the left upper border of the sternum in a middle



aged or older individual with syphilitic aortitis a continuous murmur is to be interpreted as the result of rupture of aortic aneurysm into the pulmonary artery a very rare and serious event but one which may be compatible with some weeks or months of survival. Correct antemortem diagnosis is possible even though the murmur exactly resembles that of patency of the ductus arteriosus.

4 *Arterial aneurysm* A rare cause of a continuous murmur is an arterial aneurysm which may involve the aorta one of its major branches or a peripheral vessel. Usually over such a lesion if a murmur is heard at all it is only systolic in time but there are conditions such as wide open unthrombosed cavity with rapid blood flow when the murmur continues into diastole.

5 *Coarctation of the aorta* Finally in some cases of congenital coarctation of the aorta a continuous murmur of slight to moderate intensity and not continuing throughout all diastole can be well heard over the thoracic spine.

### PERICARDIAL FRICTION RUB

Finally in cardiac auscultation we should observe the presence or absence of friction sounds due to acute pericarditis. Such sounds vary from a soft almost blowing character to extremely rough loud rasping and leathery sounds. Usually they are found in both systole and diastole and tend to be somewhat louder in systole. They may occur in systole alone which fact adds to the difficulty of their differentiation from systolic murmurs. The most common site is near the sternum especially along the left edge but they may be found anywhere or everywhere over the precordium and if loud enough they may be widely transmitted to the back and elsewhere. If marked they are attended by palpable thrills. It is often difficult in the presence of pericardial friction sounds to recognize the characteristics or even the existence of heart murmurs masked by them and if the friction sounds are of unusually soft character it may sometimes be difficult to distinguish them from murmurs. Repeated and daily observations to note the variation and gradual increase or disappearance of such friction sounds may prove necessary for their interpretation and for the diagnosis of underlying valvular or other cardiac disease.

Pericardial friction rubs are almost invariably indicative of acute pericarditis but there are occasional exceptions as pointed out by Ortiz (1933) when pericardial friction sounds or murmurs may be produced by normal pericardial surfaces rubbing against each other under unusual pressure particularly in the pulmonary valve area as in cases of pulmonary artery dilatation in thyrotoxicosis (Goodall 1920 Lerman and Means 1933) and of acute cor pulmonale due to pulmonary embolism (McGinn and White 1935).

## BIBLIOGRAPHY

## PHYSICAL EXAMINATION OF THE HEART

SEE ALSO REFERENCES UNDER GENERAL REFERENCES FOLLOWING CHAPTER 2

## Inspection and Palpation

- Dressler W *Die Brustwandpulsationen als Symptome von Herz- und Gefasskrankheiten* Wilhelm Maudrich Wien 1933 Chapter 4
- Pulsations of the Wall of the Chest" *Arch Int Med* 1937 LX 225 437 441 654 and 663
- Cardiac Topography: Pathologic Studies of the Anterior Aspect of the Heart and Its Relationship to the Anterior Wall of the Chest in Common Heart Diseases" *Am Heart J* 1940 XIX 141
- Kellogg F and White F D "The Clinical Significance of Precordial Tenderness—The Relationship of Such Tenderness to Pain" *New England J Med* 1932 CCVI 659
- Padilla, T Cossio P and del Castillo E B El latido toracico universal *Semana med* 1932 I 769

## Percussion

- Auenbrugger L *Inventum Novum ex Percussione Thoracis Humani ut Signo Abstrusos Interni Pectoris Morbos Detegendi* J T Trattner Vindobonae 1761 A facsimile of the first edition accompanied by the French translation of Corvisart the English translation by Forbes the German by Ungar and a biographical sketch by Dr Max Neuberger has been published by Josef Šafar Vienna and Leipzig 1922
- Kurtz C M and White P D "The Percussion of the Heart Border and the Roentgen Ray Shadow of the Heart A Study of One Hundred Cases" *Am J M Sc* 1928 CLXXVI 181
- Notch T M "Absence of Resonance in the Fifth Right Interspace Diagnostic of Pericardial Effusion" *Boston M and S J* 1878 XCIX 389 421
- Škoda J *Abhandlung über Perkussion und Auskultation* L W Seidel Vienna 4th ed 1850 (1st ed 1839)
- von Müller F "Aus dem Perkussionskurs" *München med Wchnschr* 1928 CXXV 6 (Translation of this paper by R. W Buck in *New England J Med* 1928 CXCIX 807)

## Auscultation Methods Sounds Gallop Rhythm

- Barie E "Sur la pathogénie du bruit de galop" *Progrès méd* 1880 VIII 595
- Butterworth J S and Poindexter C A A Multiple Channel Electronic Stethoscope for Teaching and Demonstration *Am Heart J* 1948 XXXVI 112
- Cosio P "Choque de la punta mitral" *Rev Argentina de Cardiol* 1943 X 145
- Einthoven W and Geluk M A J "Die Registrierung der Herztöne" *Pflügers Arch f d Ges Physiol* 1894 LVII 617
- Huchard, H "Contribution à l'étude clinique des tendons aberrants du cœur" *Rev de méd* 1893 XIII 113
- Kerr W J Althausen T L Bassett A M and Goldman M I "The Symballophone A Modified Stethoscope for the Lateralization and Comparison of Sounds" *Am Heart J* 1937 XIV 594
- Laennec R T H *De l'auscultation médiate ou traité du diagnostic des maladies des poulmon et du cœur fondé principalement sur ce nouveau moyen d'exploration* Brosson et Chaude Paris 2nd ed 1826 (1st ed 1819)
- Levine E A, and Harvey W P *Clinical Auscultation of the Heart* W B Saunders Co Philadelphia 1949
- Lian, C., and Dang Van-Chung "L'auscultation dorsale des souffles et frottements dans les affections cardiovasculaires" *Presse méd* 1950 LVIII 585

- Lian C and Goebelin V Les bruits du coeur foetal in utero (Étude phonocardiographique) *Arch d mal d coeur* 1938 XXXI 173
- Luisada A Variable Interval between Electric and Acoustic Phenomena in Auricular Fibrillation *Am Heart J* 1941 XXII 245
- Mannheimer E *Calibrated Phonocardiography and Electrocardiography A Clinical Statistical Study of Normal Children and Children with Congenital Heart Disease Acta Paediatrica* 1940 XXVIII Suppl II
- Calibrated Phonocardiography *Am Heart J* 1941 XXI 151
- Rappaport M B and Sprague H B "Physiologic and Physical Laws that Govern Auscultation and Their Clinical Application The Acoustic Stethoscope and the Electrical Amplifying Stethoscope and Stethograph *Am Heart J* 1941 XXI 257
- "The Graphic Registration of the Normal Heart Sounds *Am Heart J* 1941 XXIII 591
- Thayer W S On the Early Diastolic Heart Sound (the So Called Third Heart Sound) *Boston M and S J* 1908 CLVIII 713
- White P D The Clinical Significance of Gallop Rhythm *Arch Int Med* 1918 XLI 1

### Murmurs and Pericardial Friction Rub

- Bellet II Gouley B Nichols C F and McMillan T M "Loud Musical Diastolic Murmurs of Aortic Insufficiency *Am Heart J* 1939 XVIII 483
- Blain A III and Clapper M "The Cruveilhier Baumgarten Syndrome" *New England J Med* 1945 CCXXXII 647
- Bland E F White P D and Jones T II The Development of Mitral Stenosis in Young People with a Discussion of the Frequent Misinterpretation of a Middiastolic Murmur at the Cardiac Apex *Am Heart J* 1935 X 995
- Bloom H J G Venous Hums in Hepatic Cirrhosis *Brit Heart J* 1950 XII 343
- Blumgart H L and Ernstene A C Two Mechanisms in the Production of Duroziez Sign Their Diagnostic Significance and a Clinical Test for Differentiating between Them *JAMA* 1933 C 173
- Cossio P and Berconsky I "El primer ruido cardiaco y el soplo presistolico en la estrechez mitral con fibrilación auricular *Rev Argentina d Cardiologia* 1943 X, 162
- Duroziez P Du double souffle intermittent crural comme signe de l'insuffisance aortique *Arch gén de med* Paris 1861 I 417 588
- Flint A On Cardiac Murmurs *Am J M Sc* 1862 XLIV 29
- "The Mitral Cardiac Murmurs *Am J M Sc* 1886 NS XCI 27
- Goodall J S The Heart in Graves Disease *Practitioner* 1920 CV 37
- Kerr W J Harp V C Rapaport E and Bierman H II The Propagation of Murmurs and the Local Production of Vascular Murmurs in Relation to the Pulse Waves *Tr A Am Physicians* 1948 LXI 308
- Landis H II M and Kaufman I "The Occurrence of Venous Hums in Children *Arch Pediat* 1912 XXIX 88
- Lerman J and Means J H "Cardiovascular Symptomatology in Exophthalmic Goiter" *Am Heart J* 1933 VIII 55
- Levine S A "The Systolic Murmur *JAMA* 1933 CI 436
- Lian C Le souffle continu du cave supérieur *Bull et mém d l soc méd d hop d Paris* 1937 LIII 1088
- Linton R II and White P D "Arteriovenous Fistula between Right Common Iliac Artery and Inferior Vena Cava Report of Case of Its Occurrence Following Operation for Ruptured Intervertebral Disk with Cure by Operation" *Arch Surg* 1945 L 6
- McGinn S and White P D "Acute Cor Pulmonale Resulting from Pulmonary Embolism Its Clinical Recognition" *JAMA* 1935 CIV 1473
- Master A M "Apical Systolic Murmur" *Arch Int Med* 1948 LXXXI 518
- Nichols C "A Study of Syphilis of the Aorta and Aortic Valve Area *Ann Int Med* 1940 XIV 960
- Ortiz R T "Una nueva teoria de los soplos anorgánicos, frotamientos cardiaserosos *Arch Lat Am d Cardiol y Hematol* 1933 III 45

- Rivero Carvallo J M Carral R and Ramirez Jaime M H Estenosis relativa de la tricuspide *Arch del Inst de cardiol Mexico* 1951 XXI 47
- Roger H Recherches cliniques sur la communication congenitale des deux coeurs par inoclusion du septum interventriculaire *Bull d lAcad d med d Paris* 1879 VIII 1074
- Rogers O H and Hunter A Heart Murmurs and Their Influence on Longevity *Proc 30th Annual Meeting As Life Ins M Dir America* 1920 VI 173
- Stell Graham "The Murmur of High Pressure in the Pulmonary Artery" *M Chronicle* Manchester 1888 IX 182
- Wells B G Rappaport M H and Sprague H B "The Graphic Registration of Basal Diastolic Murmurs" *Am Heart J* 1949 XXXVII 586
- White P D Adams F D and Craib D Note on Cardiac Murmurs Recommendation for a Revised Terminology *Am J M Sc* 1942 CCIII 52

---

## CHAPTER 6

---

### SPHYGMOMANOMETRY NORMAL AND ABNORMAL BLOOD PRESSURE

---

Hales S *Statistical Essays Containing Haemostaticks or an Account of some Hydraulic and Hydrostatical Experiments Made on the Blood and Blood Vessels of Animals* W Innys and R Manby London 1733 Vol 2

Page 1 1 In *December* I caused a Mare to be tied down alive on her Back she was fourteen Hands high and about fourteen Years of Age had a Fistula on her Withers was neither very lean nor yet lusty Having laid open the left crural Artery about three Inches from her Belly I inserted into it a brass Pipe whose Bore was one sixth of an Inch in Diameter and to that by means of another brass Pipe which was fitly adapted to it I fixed a glass Tube of nearly the same Diameter which was nine Feet in Length Then untying the Ligature on the Artery the Blood rose in the Tube eight Feet three Inches perpendicular above the Level of the left Ventricle of the heart But it did not attain to its full Height at once rushed up about half way in an Instant and afterwards gradually at each Pulse twelve eight six four two and sometimes one Inch When it was at its full Height it would rise and fall at and after each Pulse two three or four Inches and sometimes it would fall twelve or fourteen Inches and have there for a time the same Vibrations up and down at and after each Pulse as it had when it was at its full Height to which it would rise again after forty or fifty Pulses

Hales pioneered in the estimation of venous pressure also On page 13 he wrote as follows

1 In *December* I laid a common Field Gate on the Ground with some Straw upon it on which a white Mare was cast on her right side and in that Posture bound fast to the Gate she was fourteen Hands and three Inches high lean tho not to a great Degree and about ten or twelve years old This and the above mentioned Horse and Mare were to have been killed as being unfit for service

"2 Then laying open the left Jugular Vein I fixed to that part of it which comes from the Head a glass Tube which was four Feet, and two Inches long

"3 The Blood rose in it in three or four Seconds of Time about a Foot, and then was stationary for two or three Seconds then in three or four Seconds more it rose sometimes gradually and sometimes with an unequally accelerated motion

nine Inches more on small Strainings of the Mare Then upon greater Strainings it rose about a Yard and would subside five or six Inches

Sphygmomanometry (*σφύγμος* pulsation *μετρος* thin or rare—rarity or tension—and *μετρον* measure) consists of measurement of the arterial blood pressure. It is a special method of cardiovascular study which through its introduction as a routine part of physical examination during the past generation has revealed the cause of much cardiac enlargement and failure that was previously obscure.

Two centuries or more ago and again one hundred years later actual determinations of the blood pressure of animals were made by the insertion of tubes into arteries to measure the height first to which the blood column ascended (Hales 1733) and second to which it forced a mercury column (Poiseuille 1828) but the study was applied only to animals in experimental work until much later. However long before the development of a satisfactory clinical sphygmomanometer rough attempts were made to estimate human blood pressure by measuring the weight or force needed when attached to a sphygmograph to obliterate the radial pulse (Vierordt 1855). There followed gradually the methods of pressure application by plethysmograph to the hand (Marey 1876) later by pelottes to the radial artery (von Basch 1881) and then to the brachial artery and finally by small and then larger fluid filled cuffs applied to finger or arm (Riva Rocci 1891). At last came the introduction of the present comfortable wide air filled cuffs for application to the upper arm and to the leg.

Arterial blood pressure in man is read off for convenience in millimeters of mercury instead of in centimeters of water (which would require a measuring tube over 13 times longer). The gauge is either a carefully graduated and calibrated tube of mercury or a spring pressure device with dial and needle (von Basch 1887). There are today many different models and makes of sphygmomanometers some of these are more convenient more accurate or better made than others but most of them are satisfactory provided they are checked for accuracy. Errors may creep into the use of any type of sphygmomanometer too airtight a seal of a tube containing a mercury column may for example by air compression or by relative vacuum result in errors in blood pressure readings too low during inflation of the cuff and too high during decompression completely to nullify the generally reputed greater accuracy of the mercurial sphygmomanometer. A maximal error of 3 mm of mercury may be considered permissible for sphygmomanometers in routine clinical use at pressures up to 300 mm of mercury the average error should be considerably less but great accuracy is not needed clinically since the significance of variations of a few millimeters of blood pressure is generally negligible.

Special sphygmomanometers have been devised for special purposes such as the recording sphygmomanometers which take graphic records of value

where objective data are desired for a permanent file and the oscillogram which shows at different pressure levels the fullness of the pulse in a quantitative way. The latter is especially useful in studying the peripheral circulation when there is vascular disease or obstruction. A useful new instrument introduced to register the blood pressure in the pulmonary artery and its branches the right ventricle the right atrium and the great veins during cardiac catheterization is an electromanometer devised especially for this purpose superseding the Hamilton manometer. There are various instruments and methods for the study of the venous blood pressure dependent on (1) the force applied by a pelotte (with manometer) to stop the venous flow (2) the amount of air pressure under a glass capsule measured in centimeters of water necessary to cause collapse of a vein of moderate size usually on the back of the hand or forearm (von Recklinghausen 1906 Hooker and Eyster 1908) (3) the height above the level of the right atrium in centimeters to which the forearm and hand are raised before the veins collapse (Frej 1902 Gaertner 1903) and the most satisfactory method (4) the direct reading of the pressure in centimeters of blood or of sterile normal salt solution in manometer tube connected with a needle introduced into an elbow vein at the level of the right atrium (Moritz and Tabora 1910 Griffith et al 1934 Holt 1940). A method for the graphic registration of the venous blood pressure has also been devised (Kendrew 1926). Finally methods for determining the capillary blood pressure have been introduced including (1) macroscopic blanching of the skin by pressure under a transparent capsule a method which is unsatisfactory because it includes the pressure in the smaller arterioles and venules as well (2) the more accurate microscopic method of direct observation of the blood flow in the capillaries (Lombard 1912) and most accurate of all (3) direct registration of pressure by the introduction of a fine pipette into a capillary (Landis 1930, Eichna and Bordley 1939).

The systemic blood pressure cannot be estimated by palpation alone with enough accuracy to warrant any confidence in such a procedure. Instrumental sphygmomanometry is essential. There are three techniques which as a matter of fact may be combined for the sake of greater accuracy.

The best method of clinical sphygmomanometry is the *auscultation* technique which records systolic and diastolic pressures in most cases very slightly below the actual levels as determined by direct readings from within the artery. The systolic pressure is to be read at the point when the first clear sound appears during slow decompression of the blood pressure cuff. Faint sounds due to the impact of a forceful pulsation against the closed end of the artery at the upper edge of the cuff may sometimes be transmitted to the stethoscope placed over the artery at or just below the lower edge of the cuff at any pressure above the systolic but these should be ignored. The diastolic pressure should be recorded at the point when the sound abruptly disappears or abruptly drops in intensity. Rarely the sound continues loudly to zero and the diastolic pressure must be so recorded as in some cases of marked aortic

regurgitation In 1939 a joint report was published by committees appointed by the American Heart Association and by the Cardiac Society of Great Britain and Ireland for the standardization of blood pressure readings in which there appeared a note of difference of opinion relative to a record of the diastolic pressure the American committee recommended that both the level at which the auscultatory sounds become dulled and that at which they disappear (if there is a difference) should be recorded thus 140/80 70 or 140/70 II or 140/70-70 while the British committee believed that except in aortic regurgitation it is nearly always possible to decide the point at which the change comes (either abrupt dulling or complete disappearance) and that this is the only reading that should be recorded A report by a new committee of the American Heart Association in 1951 states that it appears that the point of complete cessation is the best index of diastolic pressure

There is no practical value in attempting to record the various auscultatory phases of the pulse pressure that is in the interval between the systolic and diastolic levels except in one respect to be recounted below usually the upper most phase is one of sound the second phase which lasts normally over an interval of about 20 or 30 mm of mercury is one of murmur the third phase is one of sound again and occasionally there is a short fourth phase of diminished sound before the level of silence is reached below the diastolic pressure The one auscultatory phase that is of special importance and of practical interest is that related to the so called *auscultatory gap* In occasional cases the murmur phase may be largely or wholly absent leaving a gap of absolute or relative silence in the middle or upper part of the pulse pressure range Such a finding is most frequent in chronic hypertension aortic stenosis and marked local arteriosclerosis its exact mechanism is not clear An example of such an auscultatory gap is one of 35 mm ranging from 180 to 145 in a patient with systolic pressure of 210 and diastolic of 105 To avoid an important error in such a patient it is necessary to raise the compression of the cuff far enough above this gap so that the true systolic sounds can be heard on decompression or to check the method by either or both of the other two methods of sphygmomanometry one can easily carry out both these procedures If the auscultatory gap is not recognized there may be recorded a systolic pressure as much as 50 mm or more below what it actually is There are still other sources of error in auscultatory sphygmomanometry too low a reading when the arm is especially small and too high when the arm is very large but these errors are not great (Bordley and Ragan 1941) and in general the method is an unusually accurate bedside procedure as checked by direct intra arterial readings (Steele 1942)

A second method of sphygmomanometry the *oscillatory* is theoretically more accurate than the other technics but actually less practical because of the frequent difficulty in making the readings The systolic pressure is the point of abrupt increase in amplitude of the oscillations of the mercury column or needle of the manometer above the baseline of small pulse movements while the diastolic pressure is the first point of distinct decrease below



the maximal oscillations unfortunately however both these points may be poorly marked because of the failure of any abrupt changes. The method may be carried out visually or by a recording device (Figure 16). Its greatest value is its service as a check on the accuracy of the more practical auscultatory method except in the study of obstructive arterial disease in the extremities when it has been found that the form of the oscillographic curve is of some importance in determining variations from the normal in the vascular tree and apparently in determining the type of arteriosclerosis (Friedlander 1935).

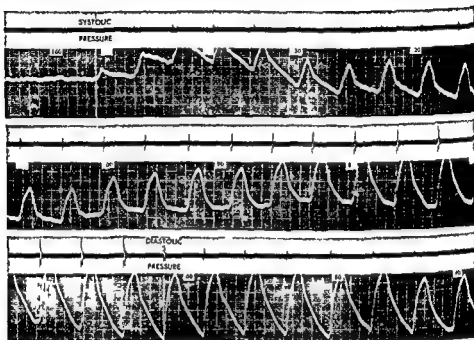


FIG 16 Human arterial blood pressure record determined by simultaneous brachial arterial tracing and phonogram at systolic pressure of 150 and diastolic pressure of 62. The first definite upstroke of the arteriogram occurs just prior to the record of the first sound. The disappearance of the truncated dip of the arterial tracing occurs at the time of the last well marked sound record (kindness of Mr M A Rappaport Sanborn Company Cambridge).

The third method of sphygmomanometry is *palpatory*. The point at which the radial pulse is first felt on decompression of the brachial cuff is recorded as the systolic pressure but this is invariably too low by about 5 to 10 mm. The method serves however as a rough check on the other methods outlined above. The diastolic pressure cannot easily be recorded by palpation and this explains why in the early days of sphygmomanometry only the systolic blood pressure was measured. Segall however a decade ago (1940) called attention to the possibility of palpating over the brachial artery the vibrations set up during the pulse pressure interval which correspond to the sounds and murmurs heard by the auscultatory method between systole and diastole.

It is of academic interest that the subject himself can roughly note the levels of systolic and diastolic blood pressure in the arm by the sensations during decompression of the cuff a thrill is felt subjectively just below the systolic pressure level and disappears just above the diastolic level

Finally there has been a revival for certain special studies of the old time direct arterial blood pressure by arterial puncture in man (Wolf and Kindler 1934) and there have been introduced in recent years methods of recording by cardiac catheterization the actual pressures in right atrium right ventricle and pulmonary artery and its branches an especially important development (Cournand et al 1944 Dexter et al 1947)

**Systemic arterial blood pressure** The blood pressure in the brachial artery of a normal adult ranges from 95 to 145 mm of mercury *systolic* depending on conditions at the time of the sphygmomanometry Age has some effect on blood pressure as recently confirmed by Master (1950) There tends to be an increase though often irregular in systolic pressure of  $\frac{1}{2}$  to 1 mm a year Thus at twenty years the systolic blood pressure normally may be 110 mm at thirty in the same person 115 at sixty 150 and so on Factors of excitement exercise eating smoking and fatigue all play a considerable role in many persons tending to elevate the systolic blood pressure moderately Nervous tension is the factor that influences blood pressure most elevating it in both normal and hypertensive individuals but especially in the latter Ayman and Goldshine (1940) found for example that in a series of hypertensive individuals 30 per cent registered a systolic pressure 40 mm or more higher in the clinic than at home and 24 per cent a diastolic pressure 20 mm or more higher The temporary hypertension that is found in many nervous but otherwise normal young men at the time of examination for athletic sports military service or insurance is well known in fact it is so common that routine blood pressure determination for admission to the army was at one time even considered inadvisable Figure 17 illustrates the wide range of the normal brachial blood pressure

The pressure varies also slightly with the respiratory phase but this is unimportant unless the respiration is greatly disturbed or the heart constricted by acute or chronic pericarditis when the pulse may become markedly *paradoxical* (see Chapter 27) the paradoxical pulse consists of marked decrease of the systolic and pulse pressures even to the point of obliteration during inspiration in contrast to the usual and normal increase of the pulse during inspiration in the case of diaphragmatic breathing

In the early morning before arising the systolic brachial arterial pressure may be 105 mm while in the same person in the midst of a busy day it may register as much as 140 strenuous exercise may send it up to nearly 200

The most important and commonest cause of abnormal high systolic blood pressure is hyperpiesia (essential or arterial hypertension) less common causes are nephritis obstruction to the renal circulation (Goldblatt 1934) convulsive seizures brain tumor tumor of the adrenal medulla (pheochromocytoma) and coarctation of the aorta (see Chapter 19) The causes of ab

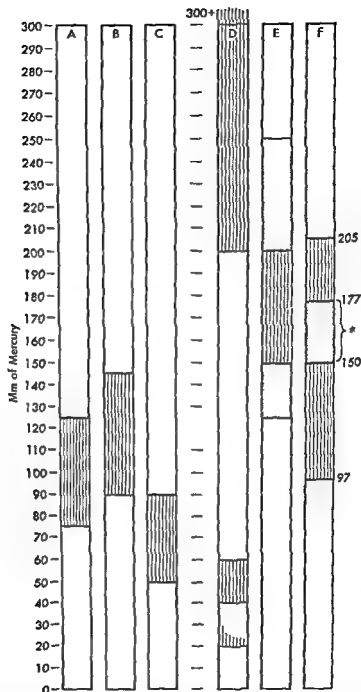


FIG 17 Diagram showing (A) the average normal adult blood pressure (125 mm mercury systolic and 75 diastolic) (B) the usual upper limits of normal pressure (C) the lower limits of normal pressure (D) the extreme upper range of pressure with hypertension and an extreme lower range of pressure with hypotension the diastolic pressure in aortic regurgitation may drop almost to 0 (broken lines) (E) the variability of the systolic pressure (from 250 to 200) and of the diastolic pressure (from 150 to 125) possible over an interval of 10 minutes in a given case of hyperpiesia

normally low systolic blood pressure are vasomotor or vascular shock Addison's disease and to a lesser degree acute and chronic constrictive pericarditis and aortic stenosis

The diastolic arterial blood pressure range is normally much less than the systolic a low reading in an adult is 60 mm of mercury and a high 90 It records the basic pressure in the circulatory system and so is fundamentally more important than the systolic pressure which is but very transient at its full height

The causes of abnormal increase of the diastolic blood pressure are the same as those recorded above for the systolic pressure The causes of abnormal decrease of the diastolic pressure are the same as for decrease of systolic pressure and in addition aortic regurgitation

In late years particularly in France much interest has been expressed in the so-called *average dynamic* or *mean effective* blood pressure which is the total pressure leveled off from the peaks and hollows of systolic and diastolic pressures that is such a pressure as would assure during a certain interval of time a steady flow of the same amount of blood as passes through a given vessel under the variations of pressure ordinarily found with each heart cycle This mean effective or average dynamic blood pressure gives to be sure a clearer idea than any other reading of the total pressure strain on the circulation but it has the defects of not taking into account the swing of the pulse pressure which is important and of being difficult to estimate accurately although Vaquez and his associates (1932 and 1933) thought that the maximal oscillation of the pulse excursion just above the diastolic level in sphygmomanometry represents with sufficient accuracy the mean pressure Moreover the mean pressure is usually close to and parallel with the diastolic blood pressure the level of which may be used as an adequate guide along with the pulse pressure Wiggers (1942) called attention again to the mean pressure but emphasized rather the importance of the pulse pressure

The pulse pressure is the difference between the systolic and diastolic pressures normally ranging in an adult at rest from 40 mm (for example with systolic pressure of 120 and diastolic of 80) to 70 (for example with systolic pressure of 140 and diastolic of 70)

An abnormal increase of pulse pressure is most commonly due either to an especially high systolic pressure in systemic hypertension (pulse pressure of 120 mm for example with systolic pressure of 220 and diastolic of 100) or to a low diastolic pressure in aortic regurgitation or marked peripheral vasodilatation (pulse pressure of 110 mm for example with systolic pressure of 140 and diastolic of 30) An abnormal decrease of pulse pressure is most commonly found in states of vasomotor shock with or without syncope (15 mm for example with systolic pressure of 65 and diastolic of 50) aortic steno-

and (F) auscultatory gap averaged in a series of 30 cases showing this phenomenon (26 with hyperpiesia 2 with hyperpiesia and aortic stenosis and 2 cases of aortic stenosis without hypertension 205 mm = average systolic pressure 97 mm = average diastolic pressure and \* = average auscultatory gap ranging from 177 to 150 mm)

sis (25 mm for example, with systolic pressure of 110 and diastolic of 85) acute or chronic constrictive pericarditis (20 mm for example with systolic pressure of 105 and diastolic of 85) or adrenal insufficiency in Addison's disease (20 mm for example with systolic pressure of 80 and diastolic of 60)

A very abnormal and clinically significant variation of pulse pressure is an alternation found when the heart rhythm is regular or after premature beat (extrasystoles) and due chiefly to a fall in systolic pressure of a few millimeters (2 or 3 to 20) every other beat this is the *pulsus alternans* a sign of serious weakness and probably of alternating strength of contraction of the left ventricle when the pulse is not excessively fast (see Chapters 8 and 30)

The blood pressure in children is less than in adults beginning at about 65 systolic and 40 diastolic in earliest infancy and rising slowly to the adult levels soon after adolescence

Finally it is important to note that the usual blood pressure readings refer to the pressure in the brachial artery on one side. It is often wise to measure the blood pressure in both arms (especially if there is suspicion of syphilitic aortitis) and to repeat blood pressure measurements several times at intervals of a few minutes if abnormal readings are found at first. The pressure in other arteries of the body varies according to their size, position and state of contraction. Thus the blood pressure in the aorta is normally greater than that in the brachial artery while that in a digital artery is considerably less. The pressure in the femoral artery is greater than that in the brachial artery for four reasons: (1) its larger size, (2) the greater bulk of soft tissue mass to be compressed in the leg, (3) the lower position of the femoral artery in the body in the upright position, hydrostatic pressure thus adding its effect, and (4) a certain amount of compensatory vasoconstriction in the lower part of the body in the erect posture. Localized vasoconstriction may occur still further to vary the pressures and sometimes exposure of a part of the body (the arm for example) to cold causes a general vasoconstriction, excessive in hypertensive cases and perhaps in potential hypertensive cases (see Chapter 31). Hardness of the arterial wall affects little or not at all the blood pressure readings made by the various indirect methods (Dameshek and Loman 1932, Ayman and Krakower 1933) although loss of elasticity of the walls of the larger arteries favors a larger pulse pressure. The act of compression of the arm may itself reflexly affect the first blood pressure levels and not simply from apprehension so that several readings are sometimes necessary. I find that it is best for this very reason to inflate the cuff at first only a little above the diastolic pressure and to record that reading during decompression before inflating to a much higher pressure to obtain the systolic reading especially in hypertensive patients.

**Pulmonary arterial blood pressure.** During the past few years one of the most desired and needed advances in human physiology has come to pass, namely the measuring and recording of the blood pressure in the pulmonary circulation by means of cardiac catheterization and electrical or optical manometer (Dexter et al 1947) (see Figure 18). In fetal life the pulmonary

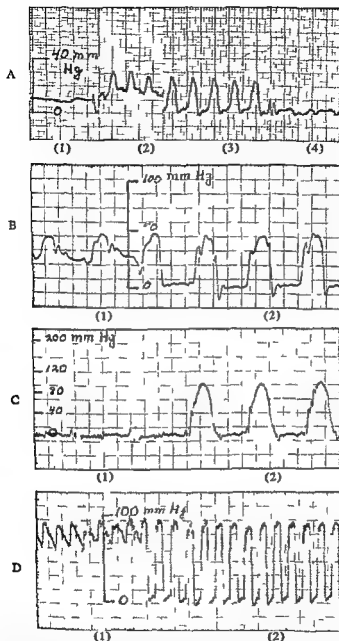


FIG 18 Blood pressure by cardiac catheterization (Kindness of Dr Gordon S Myers Massachusetts General Hospital Boston)

- A** In a normal 36 year-old man
- 1 Standardization in millimeters of mercury
  - 2 Pulmonary artery pressure
  - 3 Right ventricular pressure
  - 4 Right atrial pressure
- B** In a 24 year-old woman with mitral stenosis
- 1 Pulmonary artery pressure
  - 2 Right ventricular pressure

- C** In a 19 year-old female with pure pulmonary stenosis of high degree
- 1 Pulmonary artery pressure—abnormally low with feeble pulsations
  - 2 Right ventricular pressure—very high
- D** In a 3 year-old girl with tetralogy of Fallot
- 1 Tip of catheter overriding aorta
  - 2 Pressure in right ventricle

circulation is minimal but the right ventricle maintains through the patent ductus arteriosus the major part of the systemic circulation and is larger than the left ventricle. Soon after birth when the ductus arteriosus closes the pressures of pulmonary and systemic circuits are undoubtedly very nearly equal, hence at birth it may be said that the pulmonary blood pressure probably measures about 50 to 60 mm of mercury since that is the systemic blood pressure at this time. Normally the right ventricle fails after birth to maintain the systemic circulation and therefore the pulmonary blood pressure quickly falls below the level of the systemic pressure since the short rapidly dividing pulmonary arterial tree produces relatively little resistance. In the human adult the systolic blood pressure in the main pulmonary artery measures normally 15 to 35 mm of mercury with average of 25 mm (Figure 18) and the diastolic pressure is about 10 mm of mercury. On the other hand when the pulmonary circulatory resistance is much increased as in high grade mitral stenosis, left ventricular failure, pulmonary endarteritis, or severe chronic pulmonary disease the pulmonary arterial pressure rises considerably and may even surpass the systemic arterial pressure as further indicated by the fact that in some cases the right ventricle actually exceeds the left ventricle in size and weight. A rough check on the relationship between but not the actual levels of the systemic and pulmonary arterial pressures can be made by comparing the intensities of the aortic and pulmonary second heart sounds.

Periodic variations of pulmonary blood pressure of considerable extent have been found to occur in experimental animals and also in man with respiration. Both systolic and diastolic pressures fall with inspiration or rise with expiration, the systolic more than the diastolic. Also during cycles of apnea and hyperpnea the pulmonary blood pressure varies, the systolic pressure falling and the diastolic rising during apnea.

**Intracardiac blood pressure.** It has become possible since the publication of the third edition of this book to measure accurately and to record in man the blood pressures in the right heart chambers by intracardiac catheterization (Cournand et al. 1944) and the use of a manometer (Hamilton) or a more recently devised electromanometer (Figure 18). Normally in the human adult the right atrial pressure under basal conditions as can be attained measures from +2 or +3 to -2 or -3 mm of mercury averaging 0 mm and the right ventricular pressure ranges from +15 to +35 systolic and from +10 to +2 mm diastolic. The pressure in the left heart chambers is as yet not determinable normally but the left atrial pressure has been measured directly in the case of a congenital atrial septal defect being about +5 to +10 mm of mercury therewith and at operation in mitral stenosis being found to measure about +30 mm varying with the degree of valvular obstruction.

**Venous blood pressure.** The venous blood pressure was measured two hundred years ago by Hales who inserted a manometer directly into the jugular vein of a mare (Hales 1733)—see quotation at the beginning of this chapter. The venous blood pressure may be measured with a fair degree of accuracy as has been shown by ascertaining the actual pressure level vertically above

the level of the junction of the superior vena cava and the right atrium (approximately one third the distance through the chest from front to back at the lower border of the third right sternocostochondral junction) to which blood will rise or displace normal salt solution in a tube connected by trocar or needle with an arm vein (Moritz and von Tabora 1910 Holt 1940) or more conveniently by a spring phlebomanometer connected with the vein (Burch and Winsor 1943) In logical evolution from these cruder technics the newest and most accurate though not exactly routine method of venous blood pressure measurement is by intravenous catheter and special electro-manometer

A simple but generally adequate clinical method of determining the

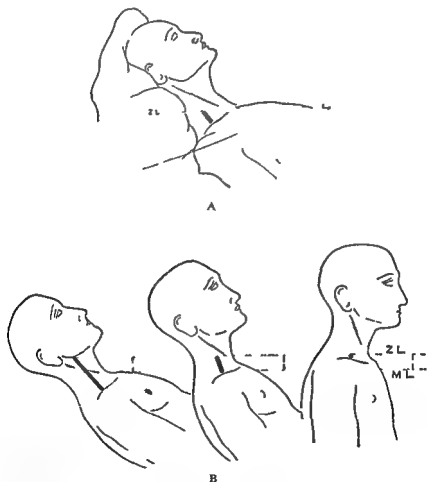


FIG 19 The level of the height of the blood column in the jugular vein (A) In a normal person recumbent (B) In a person with increased systemic venous pressure in different inclinations of the body ZL = zero level ML = manubrial line (Lewis, T Diseases of the Heart 4th ed The Macmillan Company New York 1946)



venous pressure requiring no apparatus except a centimeter scale is to measure the height above the lower border of the third costal cartilage at the right border of the sternum (level of mouth of the superior vena cava) at which the blood rises in the jugular vein with the subject sitting upright. The pressure is within the normal range that is below 10 cm the vein will not be evident and if it is very high that is above 25 cm the blood column will rise out of sight under the ear. Slight to moderate elevations can be readily measured (Figure 19). A third but now outmoded method is to determine the amount of air pressure (best measured in centimeters of water) necessary to collapse a superficial vein of moderate size in forearm or hand. An apparatus for making such a measurement has already been mentioned (page 110). Obesity, thick skin or sclerosis of the veins may make such determination difficult.

The normal venous pressure varies widely from 4 to 10 cm of water (about 1 to 6 mm of mercury). Usually it amounts to about 6 to 7 cm of water being about one half in millimeters of water of the normal arterial pressure in millimeters of mercury and therefore about 1/20 of the arterial pressure. The systemic blood pressure thus drops from say 130 to 5 mm of mercury as it progresses from brachial artery through its branches and through arterioles, capillaries and venules to a superficial vein of moderate size on the back of the hand or on the forearm. If the venous pressure by the usual method measures 10 cm or more of water it is abnormally high. Exercise may temporarily raise the pressure considerably even as high as 20 cm of water but the three conditions which are associated with abnormally high venous pressure at rest, even to 30 cm of water or more are congestive heart failure of considerable or moderate degree, acute or chronic constrictive pericarditis and venous obstruction due to thrombosis or compression. If the right ventricle remains competent while the left ventricle has failed there is pulmonary congestion and increased pulmonary venous pressure due to left ventricular weakness even though the systemic venous pressure remains normal.

A very interesting phenomenon is encountered in some cases with well marked tricuspid regurgitation without much constant distention of the systemic veins, consisting of a considerable *systolic jugular pulse* most pronounced in the deep veins in the neck. In such cases the venous pulse pressure which is usually very small or nonexistent may be marked up to 50 or 60 mm and so striking that the jugular pulse may be wrongly interpreted as the carotid pulse (White and Cooke 1939).

Another interesting phenomenon consists of the *paradoxical inspiratory filling of the jugular veins* due to the inability of the right heart chambers either because of constrictive pericarditis or severe right heart failure or of an obstructed superior vena cava to pass on the extra blood they receive from the systemic veins as the result of the increased negative intrathoracic pressure during inspiration (Hitzig 1942).

In general the venous pressure determination is not of great clinical value. Inspection of the veins to determine their degree of engorgement usually sufficing without exact measurements. It has been suggested however that a

figure of 20 cm of water of venous pressure in heart failure is a useful indication of the therapeutic need and value of venesection

We can now measure the blood pressure in the great veins in man by catheter and special manometer. It varies normally in the human adult from +3 to +5 mm of mercury with great increase when the heart fails or in chronic constrictive pericarditis. In the experimental animal the blood pressure in the great veins has been found to be much lower than that of the smaller veins dropping almost to zero in the venae cavae. This is to be expected with the slowing of the blood stream resulting from the merging of many venous channels into the narrow limits of a few for even though these few are of large caliber their total capacity is far less than that of the peripheral veins. Fortunately to aid in the return of blood to the heart there are four factors the most important of which is the intrathoracic negative pressure. The effect of intrathoracic suction during inspiration is marked and in the experimental animal may more than quadruple the actual venous pressure in the great veins to establish the effective venous pressure. For example in the dog a venous pressure of 10 mm (1 cm) of water may be increased through the action of this negative intrathoracic pressure to an effective pressure of 50 mm of water in the right atrium. Poor action of the diaphragm and disturbances of respiration limiting the negative intrathoracic pressure and especially obstruction to the venous return flow to the heart through congestive heart failure chronic constrictive pericarditis pericardial effusions or mediastinal tumors or adhesions affect very easily and obviously the venous blood return to the heart on account of the low pressure that is usual in the great veins. This is particularly true of the portal system where the blood has to flow through two sets of capillaries and enter the inferior vena cava by way of the hepatic veins which empty at a considerable angle into the vena cava. The three other factors aiding the return of venous blood to the heart are the tonus and movement of muscles which compress the veins the valves in the veins which help to keep the blood going in the right direction and on occasion as needed arteriolar and capillary dilatation to allow a speeding up of the blood flow into the veins and thence to the heart.

For a discussion of capillary blood pressure see Chapter 8 under Capillary Circulation

## BIBLIOGRAPHY

SPHYGMOMANOMETRY BLOOD PRESSURE, ARTERIAL (SYSTEMIC PULMONARY AND INTRACARDIAC) VENOUS AND LYMPHATIC

SEE ALSO GENERAL REFERENCES FOLLOWING CHAPTER 2 AND CHAPTER 19  
SYSTEMIC HYPERTENSION

### Arterial Pressure

- Alvarez, W. C. "Blood Pressures in Fifteen Thousand University Freshmen." *Arch Int Med.* 1923 XXXIII 17  
Alvarez, W. C., and Stanley, L. L. "Blood Pressure in Six Thousand Prisoners and Four Hundred Prison Guards. A Statistical Analysis." *Arch Int Med* 1930 XLVI 17

- Ayman D and Goldshme A D Blood Pressure Determinations by Patients with Essential Hypertension Difference Between Clinic and Home Readings Before Treatment *Am J M Sc* 1940 CC 465
- Ayman II and Krakower A "Influence of Sclerotic Arterial Wall on Blood Pressure Measurements Report of Case with Calcification of One Radial Artery *Arch Int Med* 1933 LII 33
- Bordley J III and Ragan C The Accuracy of Clinical Determinations of Arterial Pressure *Tr A Am Physicians* 1941 LVI 222
- Committees of the American Heart Association and Cardiac Society of Great Britain and Ireland Joint Report on the Standardization of Blood Pressure Readings. *JAMA* 1939 CXIII 294 *Am Heart J* 1939 XVIII 95 *JAMA* 1951 CXLVII 632
- Recommendations for Human Blood Pressure Determinations by Sphygmomanometers Committee under Chairmanship of Dr Carl J Wiggers *Am Heart Assoc* 1951
- Dameshek W and Loman J Direct Intra Arterial Blood Pressure Readings in Man. *Am J Physiol* 1932 CI 140
- Erlanger J A New Instrument for Determining the Minimum and Maximum Blood Pressures in Man *Johns Hopkins Hosp Rep* 1904 XII 53
- Gallavardin L and Tixier L La méthode auscultatoire moyen d'étude du mode de repletion artérielle trous auscultatoires *Paris med* 1920 X 25
- Goldblatt H et al Studies on Experimental Hypertension I The Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia *J Exper Med* 1934 LIX 347
- Hales S *Statical Essays, Containing Haemastatics or an Account of Some Hydraulic and Hydrostatical Experiments made on the Blood and Blood Vessels of Animals* W Innys and R Manby London 1733 Vol 2
- Janeway T C Important Contributions to Clinical Medicine during the Past Thirty Years from the Study of Human Blood Pressure *Bull Johns Hopkins Hosp* 1915 XXVI 341
- Korotkow Note on the demonstration of the auscultatory method of blood pressure determination in St Petersburg on October 20 1905 *Berichte d kaiserl Militarar il Akad St Petersburg* 1905 XII 395
- Marey E J Mesure manometrique de la pression du sang dans les arteres de l'homme *Physiologie experimentale* G Masson Paris 1876 p 309
- Master A M Dublin L I and Marks H H The Normal Blood Pressure Range and Its Clinical Implications *JAMA* 1950 CXLIII 1464
- Pachon V Sur la methode des oscillations et les conditions correctes de son emploi en sphygmomanométrie clinique *Compt rend Soc biol d Paris* 1909 LXVI 733
- Oscillomètre sphygmometrique à grande sensibilité et à sensibilité constante *Ibid* p 776
- Peterson L H Dripps R D and Risman G C A Method for Recording the Arterial Pressure Pulse and Blood Pressure in Man *Am Heart J* 1949 XXXVII 771
- Poiseuille J L M Recherches sur la force du coeur aortique *Magendie's jour de la physiol* 1878 VIII 272 and 1879 IX 341
- Riva Rocci S Un nuovo sfigmomanometro *Ga med di Torino* 1896 XLVII 981
- Segali H N Note on Measurement of Diastolic and Systolic Blood Pressure by Palpation of the Arterial Vibrations (Sounds) over Brachial Artery *Canad M A J* 1940 XLII 311
- Smirk F H Casual and Basal Blood Pressures IV Their Relationship to the Supplemental Pressure with a Note on Statistical Implications *Brit Heart J* 1944 VI 176
- Steele J M "Comparison of Simultaneous Indirect (Auscultatory) and Direct (Intra arterial) Measurements of Arterial Pressure in Man *J Mt Sinai Hosp* 1947 VIII 1042
- Vaquez, H and Lajoie R J "The Physiological and Clinical Study of the Average Dynamic Blood Pressure (Pression Moyenne)" *Libman Anniversary Volumes* 191 III 1163
- Vaquez H Gley P and Mouquin M Valeurs comparées de la mesure de la pression moyenne par les méthodes intra artérielle et oscillométrique" *Compt rend Soc de biol* 1933 CXIV 1305

- Vierordt K. *Die Lehre von Arterienpuls in gesunden und kranken Zuständen Begründet auf eine neue Methode der bildlichen Darstellung des menschlichen Pulses* F Vieweg u Sohn Braunschweig 1855
- von Basch ■ Ueber die Messung des Blutdrucks am Menschen *Ztschr f klin Med* 1880 II 79
- Einige Ergebnisse der Blutdruckmessung an Gesunden und Kranken *Ibid* 1881 III 507
- Der Sphygmomanometer und seine Verwerthung in der Praxis *Berlin klin Wchnschr* 1887 XXIV 179 206 224 244 and 285
- Wendkos M H and Rossman P L The Normal Blood Pressure in the Lower Extremity *Am Heart J* 1943 XXVI 623
- Wiggers C J Basic Hemodynamic Principles Essential to Interpretation of Cardiovascular Disorders *Bull New York Acad Med* 1942 XVIII 3
- Wolf H J and Kindler K. Zur Methodik der direkten Blutdruckmessung beim Menschen *Ztschr f d ges exper Med* 1934 XCIII 746

### Venous Blood Pressure

- Burch G E and Winsor T "The Phlebomanometer A New Apparatus for Direct Measurement of Venous Pressure in Large and Small Veins" *JAMA* 1943 CXXIII 91
- Eyster J A E *Clinical Aspects of Venous Pressure* Macmillan Co New York 1929
- Frey A Ueber die Bedeutung der Venendruckmessung bei der diätetisch physikalischen Behandlung der Kreislaufstörungen *Deutsch Arch f klin Med* 1902 LXXIII 511
- Gaertner G Ueber einen neuen Blutdruckmesser (Tonometer) *Wien klin Wchnschr* 1899 XII 696 and 717
- Die Messung des Drucks im rechten Vorhof *Munch med Wchnschr* 1903 L 2038 2080 and 1904 LI 212
- Griffith G C Chamberlain C T and Mitchell J R A Simplified Apparatus for Direct Venous Pressure Determination Modified from Moritz and v Tabora *Am J M Sc* 1934 CLXXXVII 371
- Hitzig W M On Mechanisms of Inspiratory Filling of the Cervical Veins and Pulsus Paradoxus in Venous Hypertension *J Mt Sinai Hosp* 1942 VIII 625
- Holt, J P The Measurement of Venous Pressure in Man Eliminating the Hydrostatic Factor *Am J Physiol* 1940 CXVX 635
- Hooker D R and Eyster J A E An Instrument for the Determination of Venous Pressure in Man *Bull Johns Hopkins Hosp* 1908 XLX 274
- Kendrew A The Graphic Registration of Venous Pressure in Man Illustrated by Some Observations on Reactive Hyperaemia *Heart* 1926 XIII 101
- Moritz F and von Tabora D Ueber eine Methode beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen *Deutsch Arch f klin Med* 1910 XCVIII 475
- White P D and Cooke W T The Recognition and Significance of Marked and Chronic Systolic Pulsation of the Deep Jugular Veins *Tr A Am Physicians* 1939 LIV 199
- Winsor T and Burch G E Use of the Phlebomanometer Normal Venous Pressure Values and a Study of Certain Clinical Aspects of Venous Hypertension in Man. *Am Heart J* 1946 XXXI 387
- von Recklinghausen H Ueber Blutdruckmessung beim Menschen *Arch f exper Path u Pharmacol* 1901 XLVI 78
- Unblutige Blutdruckmessung *Arch f exper Path u Pharmacol* 1906 LV 375 and 412 *Neue Wege der Blutdruckmessung* Julius Springer Berlin 1931
- Capillary Pressure** (See also references under Capillary Circulation in Bibliography of Chapter 8)
- Eichna L W and Bordley J III Capillary Blood Pressure in Man Comparison of Direct and Indirect Methods of Measurement *J Clin Investigation* 1939 XVIII 695
- Laddis E M Micro Injection Studies of Capillary Blood Pressure in Human Skin *Heart* 1930 XV 209

Lombard W P The Blood Pressure in the Arterioles Capillaries and Small Veins of the Human Skin *Am J Physiol* 1911-12 XXIX 335

#### Intracardiac Pressure and Pulmonary Blood Pressure

Cournand A Lauson H D Bloomfield R A Breed E S and Baldwin ■ deF "Recording of Right Heart Pressures in Man *Proc Soc Exper Biol & Med* 1944 LV 34

Dexter L Haynes F W Burwell C S Eppinger ■ C Sagerson R P and Evans J M Studies of Congenital Heart Disease II Pressure and Oxygen Content of the Blood in the Right Auricle Right Ventricle Pulmonary Artery in Control Patients with Observations on the Oxygen Saturation and Source of Pulmonary Capillary Blood *J Clin Investigation* 1947 XXVI 554

Hamilton W F Brewer G and Brotman I Pressure Pulse Contours in the Intact Animal I Analytical Description of a High Frequency Hypodermic Manometer with Illustrative Curves of Simultaneous Arterial and Intracardiac Pressures" *Am J Physiol* 1934 CVII 427

Lenegre J and Maurice P Premieres recherches sur la pression ventriculaire droite *Arch d mal d coeur* 1944 XXXVII 101

La pression ventriculaire droite *Paris med* 1945 CXXIX 21

"Recherches sur la pression sanguine dans la petite circulation chez l'homme *Acta Cardiologica* 1947 II 1

Richards D W Jr et al Pressure of Blood in Right Auricle in Animals and in Man Under Normal Conditions and in Right Heart Failure *Am J Physiol* 194 CXXXVI 115

#### Lymphatic Pressure

Drinker C K Warren M F Maurer F W and McCarrell J D "The Flow Pressure and Composition of Cardiac Lymph *Am J Physiol* 1940 CXXX 43

---

## CHAPTER 7

---

# CARDIOVASCULAR ROENTGENOLOGY

In the present edition this chapter has been profitably shortened several helpful new illustrations have been added and a number of pertinent references to the literature published since 1943 have been appended to the Bibliography

---

Williams F H Notes on X Rays in Medicine *Tr A Am Physicians* 1896  
XI 375

During the past two or three months I have been much interested in studying the X rays and with the assistance of Mr C L Norton and Mr R R Lawrence of the Massachusetts Institute of Technology who have been investigating the X ray problem in the Rogers Laboratory of Physics have tested the application of X rays to medicine in various ways Their application to surgery was soon evident

But I wish especially to direct your attention to some of the medical rather than the surgical uses of these magical rays and especially to their use with the fluoroscope in the fluoroscope with a screen of tungstate of calcium the parts of the body which are most easily passed by the X rays appear lightest on the screen those which are densest being darker The lungs are easily penetrated

The pulsations of the heart may be followed with the fluoroscope not only the ventricular but also the auricular contractions and dilatations

In the following cases the usual physical examination and that made with the fluoroscope corresponded very well

Case 1 —The first medical case I examined was that of a man with an enlarged heart (seven inches in transverse diameter) I found that the outline of the heart as seen from the front of the body through the fluoroscope corresponded in a general way to the outline drawn on the skin with percussion as a guide It was interesting to note that the heart could be made out through the man's waistcoat and two shirts

### INTRODUCTION

Cardiovascular roentgenology (*Rontgen* 1895 and *λογος* knowledge) or radiology (*radius* ray and *λογος* knowledge) has become firmly entrenched as an important part of routine study of the heart and blood vessels it ranks

fourth in value as a method of examination after history taking physical examination and electrocardiography Although in cardiovascular diagnosis the roentgen ray usually supplies but confirmatory evidence sometimes surprising and frequently useful and interesting information results from such routine study Only by this method may the size and shape of the heart be determined with certainty during life the size and shape of the left atrium aorta and lung hiluses be ascertained at all and calcification in pericardium heart muscle valves or deep blood vessels be actually visualized On the other hand

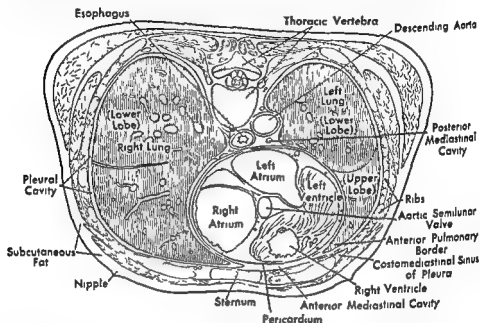


FIG 20 Anatomic drawing showing cross (horizontal) section of thorax and heart at level of the eighth thoracic vertebra (Sobotta and McMurrich *Atlas and Textbook of Human Anatomy* 1906 kindness of W B Saunders Company Philadelphia)

it must be admitted that serious heart disease may be present as discovered in other ways when no clue is given to its presence by roentgenology Also early and slight cardiovascular lesions usually escape notice in the roentgen ray film because the heart and vessels may show no definite abnormalities of size shape, or action For the most part therefore roentgenology merely reveals evidence of well established or advanced disease which is difficult or impossible to eradicate Yet it does help the practitioner of medicine appreciably in the establishment of exact diagnosis which are so essential to accuracy of prognosis and to the handling of patients with chronic heart disease

The chief difficulty in the routine application of roentgenology to the circulation lies not in the technic which can be mastered without great difficulty but in the interpretation of the normal limits of heart size shape and action and therefore in the diagnosis of slight abnormalities There are so many factors for example age size build respiration and nervousness resulting in in

dividual variations within the normal (see Figures 2, 3 and 6 in Chapter 2) that it is at present impossible to recognize them all or at least to take them all into consideration in the establishment of any satisfactory tables of measurement of size or rules about shape or action. Not only are the normal limits difficult or impossible to define accurately but in a given individual important changes may occur in heart size or shape insufficient to produce definite roentgenologic abnormalities at the time of examination which would be noted if comparative studies had been previously made. For example a heart showing in an anteroposterior teleroentgenogram a shadow area of 80 sq cm at the lower limit of the normal figures may increase in area 38 per cent before it equals even the average normal measurement (110 sq cm) and as much as 75 per cent before it equals the upper normal limit of 140 sq cm in the case of a person with a body surface area of 1.8 sq meters (Smith and Bloedorn, 1922). Successive records of heart size and shape in the same individual carefully made under varying conditions of health should be more useful than a single comparison of this individual case with a table of normal averages or a set of rules; it is however often impossible to possess information about the roentgen ray findings prior to the onset of trouble in a given case. In spite of these difficulties some rules are necessary and normal standards for measurements of size are useful if we realize their inaccuracy in application to individual patients and do not lull ourselves into a false sense of security which tends to develop from the use of figures and formulas.

## METHODS OF CARDIOVASCULAR ROENTGENOLOGY

Roentgenology of the heart includes seven procedures: the first three of which are commonly used and the last four in special cases or for some particular study. They are as follows: (1) fluoroscopic examination, (2) orthodiagraphy, (3) teleroentgenography (teleradiography), (4) (roentgen) kymography, (5) (roentgen) tomography (planigraphy), (6) visualization of heart chambers and greater and lesser arteries and veins by the injection of radio-opaque media (e.g., Diodrast) into the blood stream and (7) roentgen cinematography. At the present time the first method is used universally by the most careful workers everywhere but the other methods are rarely used together. There is a division into two schools: that employing orthodiagraphy and that using teleroentgenography. Each of these methods has certain advantages which will be presented below but in each case fluoroscopy should be and ordinarily is employed along with either orthodiagraphy or teleroentgenography. The seven procedures mentioned above will be briefly summarized herewith.

1. **Fluoroscopy** ( $\phi\lambda\epsilon\iota\iota$  to flow out,  $\rho\omicron\eta$  current and  $\sigma\kappa\omicron\pi\epsilon\iota\iota$  to examine). Fluoroscopic examination consists in the study on the fluorescent screen of the projection of the heart shadow in its various parts and in toto and with the thorax of the subject in various positions in contact with the screen. If possible the subject should in harmony with several other methods of ex-



amination—inspection percussion and auscultation—be examined chiefly in the upright position. Although the tube may be placed at a distance (2 meters or more) from the thorax for the purpose of seeing the heart and great vessels relatively undistorted by divergence of rays (telefluoroscopy), as in the case of teleroentgenography this is not essential inasmuch as accurate measurements can be obtained by orthodiagraphy nor is it practicable since so much extra energy is required (about 16 times as much as is needed with the tube at 50 cm). In fact the very magnification of the details and activity of the heart shadow by the divergent rays is helpful and one quickly becomes accustomed to the degree of distortion. Also the illumination is better with the tube nearer than at a distance especially in the oblique or lateral views.

The first position studied is most conveniently the *anteroposterior*<sup>1</sup> with the patient erect facing the observer squarely and leaning his anterior chest wall against the screen with the tube behind him. After all parts of the heart and great vessel shadows have been carefully examined in this position the contour and action of the whole heart observed the action of the diaphragm noted along with the effect of deep inspiration and expiration and the lung shadows and especially the hiluses studied the patient should then be rotated slightly to the left so that the right anterior side of the chest wall touches the screen. This is called the *right anterior* or *first oblique position*. To improve the view in this position the right hand should be held behind the head and the left hand on the left hip with the elbow forward. Still further rotation in the same direction to the *right lateral* and *right posterior oblique positions* may then be carried out if desired but this is usually not necessary study in the right anterior oblique position sufficing. In a similar way the patient is rotated to the right from the anteroposterior position until the left anterior part of the chest wall touches the screen. This is called the *left anterior* or *second oblique position*. The left hand should be held behind the head and the right hand on the right hip. Again further rotation in the same direction may be carried out if desired to the *left lateral* and *left posterior oblique positions*. And finally the patient may be examined with his back squarely against the fluoroscopic screen in the *posteroanterior position* to emphasize abnormalities of the descending thoracic aorta but this position is rarely of any value. For routine fluoroscopic examination the three positions anteroposterior right anterior oblique and left anterior oblique ordinarily suffice. An important part of the whole examination includes careful observation of heart and vessel shadows during the process of rotation from one position to another this may explain certain abnormalities the cause of which is not obvious in the positions themselves. Fluoroscopic tracings not orthodiagraphic are sometimes

Throughout the book the position of the subject in roentgenologic examination is designated according to the axis termination at the screen or film as has been customary and not at the tube thus anteroposterior signifies that the front of the chest rests against the screen "right anterior oblique" means that the right anterior chest wall is against the screen and so on. If the designation "posteroanterior" is employed in the place of the customary "anteroposterior" "left posterior oblique" must be similarly employed instead of "right anterior oblique" to be consistent but this change is neither necessary nor convenient.

made in one or more positions to study outline shapes but these are of limited value

2 Orthodiagraphy (*ορθο* straight *δια* through and *γραφειν* to write) (Montz 1902) An orthodiagram is a tracing made by the observer of the shadow of the heart and great vessels outlined against the fluoroscopic screen by the *central rays* from the roentgen tube. Its advantages are that it is very accurate if well done because the rays used are exactly parallel that observation of the heart in action allows accurate determination of the position of the apex and of junctions of atria and ventricles or of great vessels and heart which may not be possible in any other way that it requires fluoroscopic observation not always carried out with teleroentgenography and finally that it is an inexpensive method of obtaining permanent records of the shadow of the heart and great vessels. It has the disadvantages of incompleteness of total detailed picture of heart and thorax and of easy possibility of subjective errors in untrained or careless hands.

3 Teleroentgenography (*τελε* far away *Rontgen* the discoverer and *γραφειν* to write) or teleradiography (Kohler 1905) The other method in routine use for obtaining a graphic record of the heart shadow by roentgen ray from which a fairly accurate idea of heart size and shape can be obtained is teleroentgenography (teleradiography). A teleroentgenogram is a record on film or plate of the shadow in whole or in part of the heart and great vessels cast by the roentgen rays with the tube far enough away (2 meters or 6 to 7 ft) from the chest and plate for reasonable accuracy. At 6 to 7 ft the error of heart size measurement is however still appreciable the excess in transverse cardiac diameter in the normal adult being from 1.0 to 1.5 cm (8 to 12 per cent) and as great sometimes in pathologic cases as 2.5 cm the excess is still more evident in the measurement of surface area. Certain factors enter in as variables to increase or to decrease this error. They are chiefly heart size and thickness of the anterior chest wall. The larger the heart the greater is the error because the rays outlining its shadow are more divergent than are those outlining the shadow of a small heart. Even the ratio of heart size to thorax size (the cardiothoracic ratio) differs in the two technics being slightly less in teleroentgenography than in orthodiagraphy because the maximal frontal plane of the heart lies anteriorly to that of the thorax (see Figure 20 page 126). The advantages of the teleroentgenogram are as follows: (1) it is a more objective record than an orthodiagram and so less liable to subjective sources of error provided the technic be accurate. (2) it is a more complete record than the orthodiagram giving greater detail and demonstrating clearly differences in position of the thorax which differences may render inaccurate comparative measurements of heart size at different times. (3) it outlines more clearly hazy or otherwise indefinite borders. (4) it can be satisfactorily carried out by a well trained and careful technician the actual measurements and interpretation being made from the finished film by the physician.

4 Kymography (*κιμα* wave and *γραφειν* to write) About twenty years ago there was introduced (Stumpff 1931) an ingenious application of roent

genography to the study of the degree and direction of pulsation of the heart and great vessels first suggested by Sabat (1913) By the use of a grid of lead strips with narrow slits between them it is possible to record the systolic and diastolic heart and vessel borders of limited alternating sections of the heart shadow when the film moves at a uniform rate across the slits at a speed which allows several pulsations to be recorded for each of the shadow sections The grid may be placed vertically, diagonally or radially and the screen or the grid may move in any direction but the usual and most practicable and instructive arrangement is for the grid to be fixed in place with the slits horizontal and for the film to descend vertically In the resulting kymogram (see Figure 21) the innermost limits (valleys) of the excursions normally represent systole in the case of the heart shadow and diastole in that of the shadows of the great vessels while the outermost limits (peaks) normally represent diastole in the case of the heart shadow and systole in that of the shadows of the great vessels In certain disease conditions there are distortions of these pulsations an increase, for example in cases of aortic regurgitation so far as left ventricle and aorta are concerned, or of the whole heart and both aorta and pulmonary artery in thyrotoxicosis a decrease in cases of great myocardial weakness myxedema or constricting pericardium or an absence or even a reversal of the pulsation (called paradoxical) of a limited portion of the left heart shadow border at or more often just above the apex in the case of a moderately large cardiac aneurysm or myocardial infarct There is not a great deal of clinical value in roentgenkymography except in occasional confirmation or discovery of a myocardial infarct from coronary occlusion the differentiation at times of aortic aneurysms from other types of mediastinal tumors the separation of the shadows of atria and ventricles and in the course of complete study of rare or puzzling cases

An interesting new method of recording the action of the heart fluoroscopically has been introduced through Chamberlain by Henny and Boone (1945) by the use of the photoelectric cell placed over any desired portion of the heart border and connected with galvanometer Simultaneous tracings can be made of the electrocardiogram or of carotid pulse or heartbeat itself also recorded electrically Figure 22 shows examples of normal and abnormal curves which have been variously called *electrokymograms* or *electrofluorograms* Not only may records be made of the pulsation of atrial and ventricular borders and of that of the great vessels superior vena cava aorta pulmonary artery and its branches in the lung hiluses but so-called *densograms* can also be made over the main heart shadow itself and over the lungs presenting curves of the variations in the thickness of the underlying mass These electrokymograms present a clearer and simpler record of the cardiovascular motions than the films that have been customarily taken in the past (Figure 21) and will probably supersede them They have the same function however in revealing or confirming such diagnoses as myocardial infarction of significant extent and of certain aneurysmal dilatations of the great vessels Also they have been used in an effort to measure the stroke volume of the heart

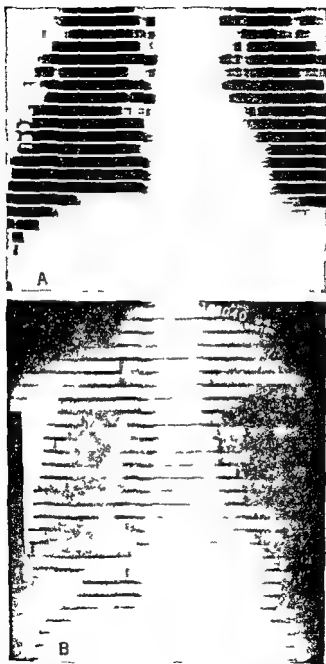


FIG 71 Kymograms (roentgenograms) of thoraces of (A) normal individual (kindness of Dr Richard Schatzki Mt Auburn Hospital Cambridge Mass) (B) case with myocardial infarct (kindness of Dr George Levene Massachusetts Memorial Hospital Boston)

**5 Roentgentomography** (*Roentgen* τόμες a cut or section and γραφειν to write) or laminagraphy (Latin *lamina* layer and γραφειν), or planigraphy (Latin *planus* a level and γραφειν) There has also been introduced in recent years a method of x ray study of the thorax that is helpful particularly in locating in three dimensions the exact position of lesions in the lungs. It is of much less importance so far as the heart is concerned but the method has not in that direction been wholly explored as yet. Tomography consists in the

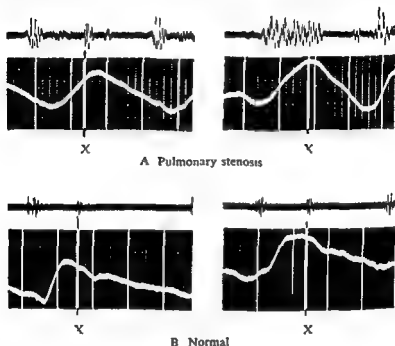


FIG 22 Electrocardiograms and simultaneous phonocardiograms taken at the pulmonary valve area of (A) two patients with pulmonary stenosis and (B) two normal individuals. Note the slow upstroke in the electrocardiogram of the two patients with pulmonary stenosis. Time = 0.04 and 0.20 second. X = time of second heart sound. (Kindness of Mr M. A. Rappaport, Sanborn Company, Cambridge.)

recording of body shadows at varying depths by exact focusing of the x rays—thus the anterior and posterior regions of the thorax may be blurred while a sharp outline is obtained of a vertical frontal plane in midthorax. It is possible by this means to obtain clearer pictures of the atria and pulmonary vessels or of the aortic arch or descending aorta.

**II Radio opaque visualization** In obscure or special cases the injection of a radio-opaque medium, most commonly Diodrast, into veins or arteries of arms or legs and very recently even directly into the ventricles themselves (Ponsdomenech and Nuñez 1951) has proved helpful in establishing a detailed diagnosis of abnormalities of blood vessels or heart chambers that might be impossible in any other way (Figures 23, 24 and 148, page 779). Considerable experience in both injection and roentgenographic technique is neces-



C

B

A

FIG 73 Roentgen films of chest of male age 40 with shadow in region of aortic arch. (A) Anteroposterior view. (B) Left anterior oblique view immediately after Diodrast injection showing filling of right ventricle and pulmonary arterial tree (C) Film a few seconds later showing filling of the left ventricle and aorta. This method of technic of Diodrast injection establishes at once the diagnosis of mediastinal tumor versus aortic aneurysm (kindness of Dr B J Walsh Washington DC)



A



B

FIG 24 (A) Diodrast x ray pictures showing the filled right ventricle and pulmonary artery in the anteroposterior and left anterior oblique views in the case of a normal heart (B) Diodrast x ray pictures showing the filled left ventricle in the case of a normal heart with diseased right lung (Kindness of Dr E R Ponsdomenech and Dr V M Nunez Havana Cuba )

sary to obtain the best results but the method should be made available in every teaching hospital and is helpful in differential diagnosis especially in congenital heart disease

**7 Roentgen cinematography** Finally a seventh method of roentgen ray study of the heart of interest from the standpoint of special investigation or teaching is that of cinematography. The most practicable way which has recently been developed consists of cinematography of the shadow as it is seen on the fluoroscopic screen (Reynolds R. J. 1934 Janker R., 1936 Rushmer 1949)

### THE SHAPE, SIZE AND ACTIVITY OF NORMAL HEART AND GREAT VESSELS STUDIED BY ROENTGEN RAY

The shape of the normal roentgen ray heart shadow is quite variable being dependent on a number of factors. The heart shadow should be outlined during quiet respiration and preferably in the sitting position for forced respiration causes abnormalities of shape and size and the standing and recumbent positions may appreciably affect the heart. Marked changes have been experimentally produced by certain respiratory efforts: the heart shadow increases considerably in size with the Muller experiment (an attempt to inspire forcefully with the glottis closed) and decreases considerably in size some times to appear like the *cor pendulosum* (pendulum heart) with the Valsalva experiment (an attempt to expire forcefully with the glottis closed) a fact of considerable interest (Crowden and Harris 1929) such experiments produce however very artificial conditions not comparable to clinical findings. The decrease in heart size during the Valsalva experiment is due to the prevention of entrance of blood into the heart by the increased intrathoracic pressure while the increase in heart size during the Muller experiment is due to the increased flow of blood into the heart resulting from the markedly negative intrathoracic pressure. So far as position of the subject is concerned the heart size and therefore its shadow may be considerably decreased in the standing position (due to much decrease in the return of blood to the heart in that posture) while there may be a considerably increased return of blood to the heart and increased content of blood in the lung vessels in the recumbent position resulting in a physiologic dilatation (Zdansky 1936). In reporting or recording roentgen views of the heart a statement should always be made as to the position of the patient and also the phase or state of respiration. To study the heart (in contrast to the lungs) it is best to make the examination and the films during very quiet respiration which is essentially midway between full inspiration and full expiration. There can be great distortion of the heart shadow with marked decrease in size if the films are taken while the breath is held in full inspiration a common practice in study of the lungs (Figure 3C page 32). For further observations concerning the range of the normal heart the reader is referred to Chapter 2.

**Anteroposterior view** In the anteroposterior view the shadow of heart and



great vessels is roughly egg shaped with apex diagonally down and to the subject's left and with the great vessels attached as a pedicle at the left side of the base (Figure 25). If the diaphragm is high the heart lies more horizontally and to the left and there is a more acute angle between it and the great vessels (Figure 3 page 32), if the diaphragm is low the heart lies more vertically and centrally in the body: seems narrower (because of this change of position and of the resultant rotation to the left) and hangs down from the great vessels with much flattened angle (Figure 3).

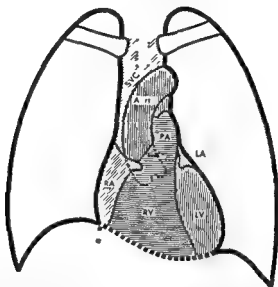


FIG 25 Drawing of normal x ray heart shadow with the various chambers and great vessels indicated (Kindness of Sir John Parkinson and the *Lancet* London)

SVC superior vena cava  
PA pulmonary artery  
RA right atrium

RV right ventricle  
LA left atrium  
LV left ventricle

The borders of the anteroposterior shadow of the heart and great vessels are three in number because of the roughly triangular shape they are right, left and inferior. Unless concealed by abnormal shadows in lungs, pleurae, pericardium or mediastinum the right and left borders are easily seen. The inferior border is seen with difficulty or not at all, concealed as it is by intra-abdominal shadows unless there is sufficient air in stomach or intestines to make its outline visible. Its whole extent is seen in only two conditions: (1) pneumoperitoneum and (2) interpolation of colon between heart and liver. The upper border of the heart at the junction of the great vessels is not seen except at its outer ends.

1 *The right border* (that to the right of the sternum of the subject, not on the observer's right) is composed of three parts. The uppermost is a rather faint, straight vertical edge extending slightly outward and to the right from below up and not always clear. It is produced by the shadow of the

right border of the superior vena cava and innominate vein at the upper part overlying the innominate artery the artery itself if dilated or prominent may form the shadow edge. The second part (next in order below) is the straight edge of the superior vena cava or more commonly the slightly convex shadow of the right edge of the ascending aorta superimposed on the superior vena cava shadow and making up a second quarter or more of the whole right border the inwardly directed curve of this aortic shadow to the left can often be made out overlying the fainter shadow of the vena cava. The third part of the right border of the heart shadow is the moderately convex shadow of the right edge of the right atrium from a point just below the mouth of the superior vena cava down to the inferior vena cava which can in rare instances be barely seen as a very short straight line quickly disappearing into the shadow of the diaphragm this right atrial shadow makes up the lower third to half of the right border of the shadow of the heart and great vessels.

2 The left border of the shadow of the heart and great vessels is considerably longer than the right (about 50 per cent longer) and is made up normally of four parts. The uppermost part is a short convex curve close to the apex of the whole shadow and is directed up toward the left shoulder of the subject it is variable in prominence and is due to the shadow of the upper and left edges of the aortic arch and beginning of the descending aorta. The second part is a slightly convex curve just below usually slightly longer than the first but making a considerable angle with it directed downward from the subject's right to his left and often almost continuous in direction with the left border of the main shadow of the heart itself which lies below the trunk of the pulmonary artery and its left main branch cause this convexity. Third and next below for a very short distance and forming a straight or slightly convex line lies the left border of the left atrial appendage often not distinguishable from the edge below it unless its presystolic pulsation happens to be seen or there is marked left atrial bulging. And fourth the major part, two thirds to three fifths of the left heart and great vessel shadow border is caused normally by the left ventricular shadow forming a slightly or moderately convex line sloping to the subject's left from above downward and becoming more definitely curved downward as the apex is approached.

3 When the lower border of the heart shadow is visible it is made up of the apex and lower border of the left ventricle on the extreme left then for one half to three quarters of the distance to the subject's right heart border it is caused by the right ventricular shadow and for the rest of the distance to the right of the midsternum by the right atrium. However varying positions of the heart alter these relations for example in the case of the drop or vertical heart little or none of the right atrium forms the lower border of the heart shadow. When this lower border is visible it is slightly convex near the apex but fairly straight from there on.

The peak of the heart and great vessel shadow is blunt and obscure except where the aortic arch is visible on the subject's left, but in some cases the aorta crossing above the pulmonary artery to form the arch can be seen. This

peak of the great vessel shadow ■ more cylindric than cone shaped being at elongated pedicle

**Right anterior oblique view** In the right anterior or first oblique view (Figure 26) the shadow of the heart and great vessels shows in front from below upward the convex curve of the right ventricle if the subject is sufficiently turned if the rotation is slight the left ventricle may be seen At the upper third of this anterior edge the pulmonary artery and aortic shadow appear and the latter sweeping over in a long curve loses itself in the shadow

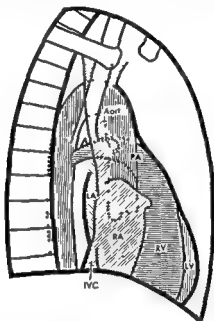


FIG 26 Drawing of shadows of normal heart and great vessels in right anterior oblique position with various chambers and great vessels indicated (Kindness of Sir John Parkinson and the *Lancet* London)

IVC inferior vena cava  
PA pulmonary artery  
LA left atrium

RA right atrium  
RV right ventricle  
LV left ventricle

of the spine posteriorly Under this aortic shadow and at the upper part of the posterior border of the heart shadow lie the bifurcations of the trachea and of the pulmonary artery Below this are the straight or slightly convex borders of the two atria the left above the right and the latter extending down to the diaphragmatic shadow where the inferior vena cava may be just visible The anterior and posterior mediastinal spaces should be clear and the trachea and bronchi are usually to be seen The left ventricle ■ concealed at the back of the heart shadow in this position (note Figure 20)

**Left anterior oblique view** In the left anterior oblique view (Figure 27) the heart is seen as it were almost in sagittal section both ventricles and both atria being evident the two former making up the lower two thirds of the

heart shadow the right in front and the left in back and the two latter making up the upper third of the shadow, the right in front and the left behind. The aorta arches over the top its whole extent may be seen better in this view than in any other if it is sclerotic but normally the outline of the lower border of the aortic arch is made out with great difficulty if at all. Below the aorta at the upper limit of the heart shadow posteriorly is the pulmonary artery. Between the aortic arch and the pulmonary arch is a clear space called the aortic window.

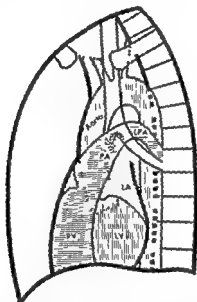


FIG 27 Drawing of shadows of normal heart and great vessels in left anterior oblique position with various chambers and great vessels indicated (kindness of Sir John Parkinson and the *Lancet* London)

PA pulmonary artery  
LPA left pulmonary artery  
LA Left atrium

RV right ventricle  
LV left ventricle

Note aortic window (open space) separating aortic arch from pulmonary arteries

The chief advantage of the oblique views lies in the study of aorta and left atrium this is especially true of the left anterior oblique view which has been regarded by some workers as the most valuable of all views in establishing the comparative size of the various parts of the heart.

**Lateral view** The lateral view is of value in measuring the depth that is the anteroposterior diameter of the heart for its own value or for use in a formula to estimate the heart volume (see page 146). This diameter is taken at right angles to the long axis of the heart.

**Normal size of heart and great vessels** Certain measurements of heart size made on the orthodiagram or teleroentgenogram are in routine use and are of some value in spite of the wide normal variations and of the difficulty or

impossibility of judging accurately either the presence or degree of slight cardiac enlargement by such measurements. It is obvious for example that increase in heart volume is represented by a far smaller increase in measurements of diameters or of area: an increase of 100 cc of volume would add only about 15 sq cm to the area in the anteroposterior view.

The following are the more useful teleroentgenographic measurements and but two obtained in the anteroposterior view to make correction for orthodiagraphic records subtract 10 per cent. Other measurements of all sorts have been suggested but only the more important or interesting will be mentioned here.

The *transverse diameter of the heart* (T or H—Horizontal—of Bordet) is made up of the sum of the maximal distance of the right border from the midsternum (MR) and of the maximal distance of the left border from the midsternum (ML). Normally this diameter measures in the adult from 10 to 15 cm depending on the size of the person and from 6 to 10 cm in the child.

The *long diameter of the heart* (L) is the distance from the junction of right atrial and great vessel shadows on the right border to the point of the cardiac apex. Normally this diameter measures in the adult 10 to 15 cm more than the transverse diameter on the average therefore from 11 to 16 cm and in the child 0.5 to 1.0 cm more than the transverse diameter that is from 7 to 11 cm.

The *broad diameter of the heart* (B) is made up of the addition of the lengths of two perpendiculars dropped from the line of the long diameter to the junction of right atrial shadow and diaphragm on the right (BR) and to the junction of left atrial (or left ventricular) and pulmonary artery (or right ventricular) shadows on the left (BL). Normally this diameter measures in the adult 8 to 11 cm and in the child 5 to 8 cm.

The *left ventricular chord* (LV or VG—*ventricule gauche*—of Bordet) subtends the arc of the left ventricle from its upper extremity on the left to the apex. Normally this chord measures in the adult from 5 to 9 cm and in the child from 3 to 5 cm.

*Width of the great vessels* (GV). A measurement of some interest but not of much value is that of the width of the shadow made by the great vessels at the widest part of the pedicle of the heart shadow usually at the level of the second intercostal space horizontally measured. This measurement varies not only with dilatation of the aorta and superior vena cava but also with kinking of the aorta when it is very tortuous from arteriosclerosis or pushed upward by an enlarged or horizontally placed heart resting on a high diaphragm. Normally the width of the great vessels measures 5 to 7 cm in the adult and 3 to 4 cm in the child of ten years of age.

The *diameter of the aortic arch* (Ao) taken in the anteroposterior position is a measure of the length of the horizontal line drawn from the outermost bulge of the aortic shadow at the left of the midsternum to the shadow of the barium filled esophagus which passing under the aortic arch outlines

the right border of the descending portion of the arch a subtraction of 2 mm is necessary to take into account the thickness of the wall of the esophagus if this line is not horizontal the measurement is inaccurate because of abnormal relative positions of aorta and esophagus. The normal upper limit of this aortic arch measurement in the adult should not be over 3 cm. The diameter of the aorta at the beginning of the arch (Ao or Asc A) is found in the right anterior oblique position by measurement of the horizontal line joining the two sides the anterior edge outlined by the anterior mediastinum and the posterior edge by the trachea. Two millimeters comprising the thickness of the tracheal wall should be subtracted from this measurement to obtain the true aortic diameter which should normally range from 2.5 to 3.5 cm at this point. An unsatisfactory measurement of the diameter of the aortic arch is that obtained in the left anterior oblique position namely the vertical distance from top to bottom of the aortic arch shadow at the top of its curve. This in the normal adult averages 3.0 to 3.5 cm. It is unsatisfactory because often the lower border of the aortic arch is seen only with great difficulty if at all unless a contrast medium has been injected.

The *depth of the heart* (or anteroposterior diameter) is measured at right angles to the long axis of the heart in the lateral view at the point of greatest thickness. Normally this measures two thirds to three quarters of the transverse diameter of the heart in the anteroposterior view (Roesler 1934) or in the adult 6.5 to 10.5 cm and in the child 4 to 7 cm. Its chief value is in checking the significance of the measurement of the diameters of the anteroposterior view and in forming a part of a formula for estimating the volume of the heart.

A standard but often unsatisfactory measurement of chest size for comparison with heart size is the *internal diameter of the thorax* (Th) at its widest point just above the diaphragmatic attachment.

The *area of the heart shadow* (A) which does not include the great vessels is measured after arbitrarily joining by slightly convex lines the outer and visible ends of the upper and lower borders. The area can be easily determined by the use of a planimeter less easily by superimposition of cardiac outline on paper specially ruled with centimeter squares or by weight of paper cut out exactly to fit heart shadow compared to weight of 100 sq cm of the same paper (Mazer 1942) but most easily by nomogram based on the broad and long diameters of the heart (Ungerleider and Gubner 1942). The area of the normal heart shadow in the anteroposterior teleroentgenogram measures in the adult from 65 to 145 sq cm averaging 112 for males and 100 for females and in the newborn from 17 to 20 sq cm.

Finally attempts have been made to obtain a measurement of *heart volume* by the use of various formulas. Such measurement theoretically ideal has not as yet proved practical it will be discussed below. The range of the normal heart volume in the adult male is from 400 to 900 cc and in the adult female from 300 to 550 cc (Comeau and White 1939).

When the heart lies horizontally the transverse and long diameters become more nearly the same. A correction of the normal transverse measurement for

position has been suggested based on the angle between the lines of these two diameters and utilizing the surface area of the body for standard comparison. The smaller the angle and also of course the larger the surface area of the body the longer should be the transverse diameter. Figure 28A shows the average normal measurements of the transverse diameter with these two variables charted and Figure 28B shows the surface area of the subject in square meters calculated according to height and weight. This latter figure may also be used in calculating the normal vital capacity (see Chapter 10).

The relationship of depth or thickness of the heart to the size of the area and diameters on the frontal plane silhouette is of much interest and of fundamental importance. The flatter the chest the less is the depth of the heart and the greater are the various frontal plane measurements the deeper the chest the smaller should be the frontal plane measurements of the heart (Roesler 1934).

**Calculation of normal heart measurements** The simplest most practical and most reliable heart measurements are those of the *diameters* transverse long broad and anteroposterior (or depth). They are measured directly and usually with ease. The transverse diameter is the most useful of the diameters the anteroposterior the least used. Tables slide rules and nomograms (Hodges and Eyster 1926 Ungerleider and Gubner 1942 Kurtz 1943) have been constructed for the calculation of the normal average transverse diameter according to height and weight for comparison with the actual finding in any given case (Figure 29). The range of normal varies from 10 per cent above to 10 per cent below this figure a fact that materially diminishes the value of this as well as all other roentgen measurements as utilized at present (see Chapter 2).

A roentgen measurement of heart size very popular in the past but generally unreliable and unsatisfactory because of the extremely wide range of the normal (from 33 to 57 per cent) is the so-called *cardiothoracic ratio* or *heart lung quotient* using a fraction in which the numerator is the transverse diameter of the heart and the denominator the internal diameter of the thorax the normal range is from 0.33 to 0.55. Not only is the range of normal too wide because of the poor correlative standard of thoracic width (height and weight are preferable although also open to objection) but the cardiothoracic ratio has in addition the defect inherent in the transverse diameter which does not take into consideration the broad diameter of the heart which may be considerably increased in mitral stenosis for example without increase in the transverse diameter. There are however rare persons of unusual build short and light with wide chests in whom the cardiothoracic ratio applies more accurately than do other formulas.

The other diameters especially the long and the broad are useful as supplements of the transverse but are more readily considered in connection with area measurements either made directly or by formula as in the nomogram in Figure 29.

The measurement of the *area* of the heart shadow in the frontal silhouette

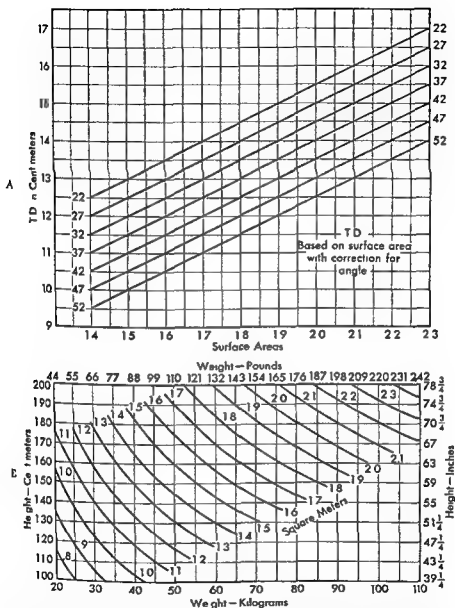


FIG 78 Corrections for angle of heart's axis (A) Chart for the determination of the normal variation of the measurement of the transverse diameter (TD) of the roentgen heart shadow with varying height and weight (Smith and Bloodorn *U.S. Naval M. Bull.* 1917 XVI 719)  
(B) Chart for the determination of the surface area of the body from the height and weight (Dubois E. F. Fig. 19 on page 119 of *Basal Metabolism in Health and Disease* 2nd ed. Lea & Febiger Philadelphia 1927)



that is on the usual anteroposterior teleroentgenogram or orthodiagram is theoretically sounder than that of the diameters and actually it has been found to be fairly satisfactory when compared to the size of the individual as in the formula *orthodiagraphic cardiac area in sq cm = age × 0.0704 - stature × 0.8668 + weight × 0.337 minus the constant 63.8049* (Hodges and

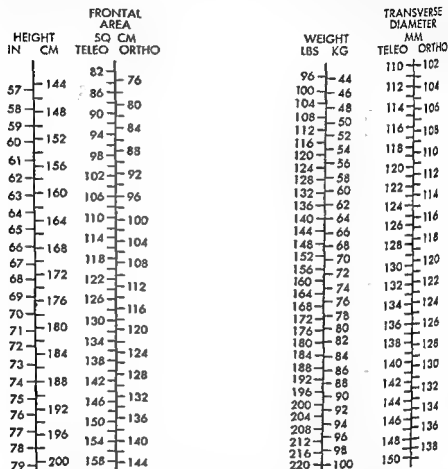


FIG 29A Nomograms for determination of the frontal area and transverse diameter of the normal heart shadow of teleroentgenogram and orthodiagram predicted from height and weight

The Hodges Eyster formula applied by Kurtz. The roentgen films and orthodiagrams were made during quiet respiration. Add 10 per cent of patient's age to predicted transverse diameter. The measurement of the area by teleroentgenogram is 11 per cent greater than the area of the heart shadow by orthodiagram. The transverse diameter of the heart shadow in the teleroentgenogram is 8 per cent greater than that of the orthodiagram.

In making the determination a straight edge joins the figures for the height and weight of a given case. The points of intersection of this line with those recording area and transverse diameter are then read off as representing the expected average area and with the addition of 10 per cent of the patient's age the expected average transverse diameter. An allowance of 10 per cent extra is to be considered the extreme upper limit of normal. (Kindness of Dr Chester M Kurtz, Madison Wis.)

Eyster 1924) Thus for a person fifty years old 173 cm (5 ft 8 in) tall and weighing 70 kg (154 lb) the orthodiagraphic cardiac area should be normally 112 sq cm. If the heart area is found to be 7 sq cm larger than the predicted area by this formula the chances are 3 to 1 that the heart is actually enlarged; if the actual area is 14 sq cm larger than the predicted area the chances of cardiac enlargement are 10 to 1 and if 21 sq cm larger the chances are 45 to 1. A simple calculation by slide rule or nomogram (Figure 29) can be made to determine the expected normal at any age, height and weight for either orthodiagram or teleroentgenogram.

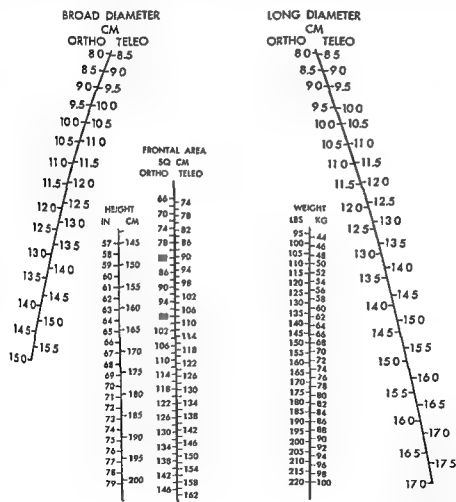


FIG 29B. Area of heart shadow of orthodiagram and of teleroentgenogram determined from the long and broad diameters (the predicted area from height and weight)

$A = \frac{\pi}{4} \times L \times B$  (Kindness of Dr Harry Ungerleider Equitable Life Assurance Society of the U.S. New York City)

The ideal measurement of heart size by roentgen ray should be that of *volume* because of the established fact that the heart normally and abnormally varies considerably in all its diameters. As yet however the determination of the heart volume has not been routinely introduced and under present conditions it is not likely that it can be satisfactorily applied clinically for two reasons: (1) in the first place there is far too wide a range of normal heart size using recognized correlations and (2) the technic is not easy or accurate especially in the very cases of cardiac enlargement in which the physician is most interested. Various formulas have been suggested especially those of Bardeen (1918), Kahlstorf (1932), Benedetti and Bollini (1934), and Strandquist (1935). Bardeen's formula is  $0.53 \times A$  (*teleroentgenographic silhouette area*)<sup>3/2</sup> = *V* (*volume*) in a case with area of 100 sq cm the heart volume would be calculated to be 530 cc by this formula which is probably not far from the true volume of a partially filled heart in an adult of average size. Kahlstorf's formula is  $V$  (*volume*) =  $0.63 \times$  *orthodiagrammic silhouette area of frontal plane heart shadow*  $\times$  *maximum anteroposterior diameter* (*D*). If the area in a given case equals 100 sq cm and the anteroposterior diameter equal 8.5 cm the heart volume according to this formula would be 535 cc. Benedetti and Bollini have published a formula for the tridimensional heart size  $V_c$  (*vol*) =  $0.45 \times$  *the long diameter of the heart in the anteroposterior orthodiagram*  $\times$  *the broad diameter of the heart in the anteroposterior orthodiagram*  $\times$  *the depth of the heart in the lateral orthodiagram* a case with long diameter of 12 cm transverse diameter of 10.5 cm and depth of 9 cm would thus have a volume of 510 cc. Strandquist gives the following formula using orthodiagrammic measurements  $V$  (*volume*) =  $2/3 \times 1/2 L$  (*long diameter*)  $\times 1/2 B$  (*broad diameter*)  $\times S$  (*depth of heart in sagittal view*) using teleroentgenographic measurements he suggests  $V = 0.42 L \times B \times S$ . Thus using the last named formula in the case of a normal adult with  $L = 14$ ,  $B = 10$  and  $S = 9$  we find that  $V = 529$  cc. One must of course correlate the heart volume determined by any formula to body size and also to the degree of filling of the heart under some standard condition. As has been noted already, the filling of the heart and hence its volume will vary greatly under certain conditions probably changing at least 100 per cent in passing from the Valsalva experiment to the Muller experiment (see page 135).

Careful clinical studies made at the Massachusetts General Hospital (Comeau and White, 1939 and 1942) have demonstrated the inadequacy of all these various measurements chiefly because of the wide range of the normal heart size and shape in connection with all recognized correlations such as height and weight and body surface area. It is hoped that other standards representing types of body build may some day prove more suitable and permit more reliance on roentgen measurements. At present the simple transverse diameter of the heart related to body height and weight following Hodges and Eyster's tables seems the most satisfactory measurement of heart size with area a moderately close second. The reason why area is not better as it should be on first thought is that a considerable part (the upper and lower

borders) of the circumference of the heart shadow (in the anteroposterior view) has to be arbitrarily completed before the measurement by planimeter can be made. This same reason plus the frequent difficulty of sharp measurement of the depth diameter of the heart (as well as the great range of normal) makes the volume calculation unsatisfactory. The commonly used cardiothoracic ratio is in general too crude and its normal limits are far too wide, however it can be useful in rare cases who are not tall but who have very wide chests.

Finally it has been suggested that in addition to inspection of the size and density of the hilus shadows of the lungs in the anteroposterior heart shadow a measurement of their breadth be made. This is much better done on the right side the measurement being actually that of the lower main branch of the right pulmonary artery. Normally this hilus shadow measures 11 to 14 mm broad (average 13 mm) with the tube 1.5 meters away from thorax and screen. If it is over 15 mm broad it is abnormal.

Taken altogether these measurements of heart and aortic size should be interpreted very freely they are probably better than no measurements at all when they are so interpreted. But when an attempt is made to fit each case within narrow so-called normal standard limits it is better to discard all measurements and to rely simply on general impressions and experience. Some physicians do this now and are as successful in diagnosis as are other physicians who rely on extensive tables or formulas.

**Activity of the normal heart and great vessels as seen roentgenologically**  
Normally the atrial contractions precede by a small fraction of a second (about 0.15 second) the contraction of the ventricles. Theoretically this interval is sufficient to allow the atrial contractions to be visible in fluoroscopic examination but often this is not actually possible the vigorous ventricular action coming so soon after that of the atria that they both seem to share but a single motion. If however the atria are enlarged and vigorous and very close attention is paid to the right atrial and left ventricular borders in the anteroposterior view or to the left atrial and left ventricular borders in the left anterior oblique view it is possible to distinguish a retraction of the atrial border ahead of the ventricular. This separation becomes more and more obvious and marked with increasing delay in atrioventricular conduction and in complete block the atrial contractions may be clear. Often atrial fibrillation, weak or scant atrial contractions or obscure outlines prevent any evidence of atrial action at all in fluoroscopic examination and if there is free mitral or tricuspid regurgitation ventricular systole may be vigorous enough to cause an outward movement of the atrial borders.

**Ventricular action** also varies very much normally in force, extent and character. In repose it tends to be quiet, slight to moderate in fullness and slow with leisurely (that is relatively long) systole. After exertion and with excitement it is active, rapid and forceful with shorter systole. With the especial increase of circulation due to exertion the contractions are fuller as well as more rapid. In the upright position a vertical heart may beat rapidly and force-

fully laboring to send out blood which is coming to it in too small an amount. Firm abdominal pressure by relieving this situation slows and calms the heart action. When the ventricles contract apex and base of the heart approach each other the base moving down in this process even more than the apex moves up and the heart rotates to the right so that the apex of the left ventricle strikes the chest wall. This composite movement is more obvious in the case of the horizontally placed heart than in that of the vertical heart. It can be made more evident in either case by increasing the fullness of contraction by exercise. The pulse of the ventricles is a single rapid process not accompanied by a wave of contraction the wave like change that is sometimes seen passing down over the base of the left ventricle with systole is simply the actual movement of the base that is the atrioventricular junction, toward the apex as the heart contracts.

The *great arteries* that is the aorta and pulmonary artery are seen to dilate with systole as the blood is pumped into them this results in a vertical rocking or seesaw motion of the heart shadow with retraction below and outthrust above especially evident along the left border. This motion can be increased by exercise or excitement and in itself is not abnormal except as it may be much magnified under certain conditions as for example with aortic or pulmonary regurgitation. Pulsation of the great veins is not normally visible except for that of the superior vena cava in the recumbent position when atrial and ventricular waves are seen. A slight pendulous movement of the heart is due to respiration and not to heart action itself. Moderate pulsation of the lung hiluses due to the presence there of the larger branches of the pulmonary artery may be normally visible in thin adults or in children with increased heart action.

Roentgenkymography, electrokymography and roentgencinematography already described above are methods that may be employed to obtain permanent records of cardiac and vascular pulsation and thus to supplement fluoroscopy.

#### ABNORMALITIES OF SIZE SHAPE AND ACTIVITY OF HEART AND GREAT VESSELS STUDIED BY ROENTGEN RAY

The various abnormalities of the roentgen shadows of the heart and great vessels will be presented in appropriate chapters later in the book with particular relation to etiologic types and structural defect. The index may be consulted for quick reference to the special pages concerned. A few further notes should be added however in concluding the present chapter.

*Disorders of cardiac rhythm.* Although it is possible to diagnose such disorders of mechanism as premature beats, paroxysmal tachycardia, atrial fibrillation and even flutter, atrioventricular nodal rhythm and heart block by fluoroscopy, their identification and analysis are so much easier and more complete by other methods of examination especially electrocardiography that fluoroscopy is not a procedure of choice for their study. Their presence may be first noted in roentgen ray examination but details are sure to be missed

With tachycardia whether of physiologic or pathologic nature the heart shadow often decreases in size with bradycardia the reverse is usually true

**Calcification** Calcification may be noted in *heart arteries* or *pericardium*. It is most commonly and easily seen in the peripheral arteries especially in those of the legs. The tortuous course of the calcified vessels may be found with or without symptoms or signs of faulty circulation in muscles and skin such as intermittent claudication or gangrene. The next most common site of visible calcification is the thoracic aorta the whole vessel may be clearly outlined by general calcification (Figure 144 page 749) or there may be irregularities of density due to plaques. The abdominal aorta may also be sufficiently calcified to be visualized by roentgen ray especially if there is much air in the overlying gastrointestinal tract. Uncommonly there may be enough calcification of a diseased pericardium to be visible by roentgen ray (see Figure 140 page 730) such calcification is best noted end on in the oblique or lateral views. Sometimes calcified valves (especially in calcareous aortic stenosis) or areas in the myocardium (old infarcts) or even calcified mural thrombi may be seen. Calcified coronary arteries may be recorded on the roentgenogram or seen fluoroscopically but only in cases of advanced disease which is usually clearly evident on clinical examination here the calcification is simply a gravestone covering tissue long dead

**Pressure on bones** Changes of bones due to erosion or deformity caused by heart or blood vessels are to be looked for. A very large heart in early childhood may cause a bowing out of the left anterior chest wall. With coarctation of the aorta the ribs may be eroded by the widened intercostal arteries as a result of the attempt of the body to compensate for this congenital defect (see Figure 77 page 332) in some cases the diagnosis of this congenital defect has been first suggested by roentgen ray examination. Vertebrae sternum and ribs may be found to be eroded by the pressure from aneurysms of thoracic or abdominal aorta or of the main branches of the thoracic aorta

**Fat shadows** At the apex there is often a considerable triangle of fat lying in a fold between pericardium pleura and diaphragm (epipericardial fat) this is of less density than the heart shadow (see text and Figure 7 pages 38 and 39) and should not be confused with it to occasion an incorrect diagnosis of cardiac enlargement such as has frequently happened (McGinn and White 1936). This mass of fat may be as wide in transverse diameter as 2 cm. it can be easily differentiated on fluoroscopy especially on deep inspiration and by contrast films. There may be fat also at the right heart border but of lesser amount

## BIBLIOGRAPHY

## CARDIOVASCULAR ROENTGENOLOGY

SEE ALSO REFERENCES UNDER CHAPTERS 23 OTHER ETIOLOGIC FACTORS AND  
RELATIONSHIPS 25 ABNORMALITIES OF MYOCARDIUM AND OF HEART  
CHAMBERS 26 VALVULAR DISEASE 27 PERICARDIAL DISEASE  
28 VASCULAR DISEASE AND 34 HEART BLOCK

- Assmann H *Die klinische Röntgendiagnostik der inneren Erkrankungen* F C W Voelke  
Leipzig 4th ed 1928
- Bardeen C R "Tables for Aid in the Determination of the Relative Size of the Heart  
by Means of the Roentgen Ray" *Am J Roentgenol* 1917 IV 604
- Determination of the Size of the Heart by Means of the X rays *Am J Anat*  
1918 XXIII 423
- Benedetti P and Bollini V "Ricerche cliniche sulla morfologia del cuore. Nota  
seconda. L'ortocardiogramma in proiezione laterale e la determinazione del valore  
cardiaco" *Endocrinol e pat cost* Bologna 1934 IX 575
- Bordet E and Fischgold H *La Radiokymographie du Coeur et des Vaisseaux* Masson  
et Cie Paris 1937
- Castellanos A, Pereiras R and Garcia A "La Angio-cardiografia radio-opaca" *Arch  
Soc estud clin Habana* 1937 XXXI Nos 9-10
- Comeau W J and White P D "An Evaluation of Heart Volume Determinations by  
the Rohrer-Kahlstorf Formula as a Clinical Method of Measuring Heart Size" *Am  
Heart J* 1939 XVII 158
- "Body Build and Heart Size: Study of 20 Pairs of Identical Twins and 15 Pairs of  
Unrelated Individuals with Similar Body Height and Weight" *Am Heart J* 1939  
XVII 616
- A Critical Analysis of Standard Methods of Estimating Heart Size from Roentgen  
Measurements *Am J Roentgenol* 1942 XLVII 665
- Crowden G P and Harris H A "The Effect of Obstructed Respiration on Heart and  
Lungs: Its Clinical Importance in Radiography" *Brit M J* 1929 I 439
- Danzer C S "The Cardiothoracic Ratio: An Index of Cardiac Enlargement" *Am J  
M Sc* 1919 CLVII 513
- Dielen H *Herz und Gefasse im Röntgenbild mit einem Beitrag über Röntgenbefunde  
bei den Arrhythmien des Herzens* von A Weber J A Barth Leipzig 1923
- Edeiken J "A Comparison of the Orthodiagram with the Teleoroentgenogram" *Am  
Heart J* 1940 XX 77
- Gott T and Rosenthal J "Ueber ein Verfahren zur Darstellung der Herzbewegung  
mittels Röntgenstrahlen (Röntgenkymographie)" *Munch med Wchnschr* 1912 LIX  
7031
- Groedel F M *Die Röntgendiagnostik der Her- und Gefusserkrankungen* H Meusser  
Berlin 1912
- Gubner R, Crawford J H, Smith W A and Ungerleider H E "Roentgenkymog-  
raphy of the Heart: Its Clinical Applications and Limitations" *Am Heart J* 1939  
XVIII 729
- Hodges F J and Eyster J A E "Estimation of Transverse Cardiac Diameter in Man" *Arch  
Int Med* 1926 XXXVII 707
- Hodges F C and Eyster J A E "Estimation of Cardiac Area in Man" *Am J  
Roentgenol* 1924 XII 257
- Janker H "Roentgen Cinematography" *Am J Roentgenol* 1936 XXXVI 384
- Kahlstorf A "Über eine orthodiagraphische Herzvolumenbestimmung" *Fortschr a d  
Geb a Röntgenstr* 1932 XLV 123
- "Über Korrelationen der linearen Herzmaße und des Herzvolumens" *Klin  
Wchnschr* 1933 XII 262
- Köhler A "Die Herstellung fast orthodiagraphischer Herzphotogramme mittels Rönt-  
geninstrumentarien mit kleiner Elektrizitätsquelle" *Wien klin Rundschau* 1909  
XIX 279
- "Teleroentgenographie des Herzens" *Deutsch med Wchnschr* 1908 XXXIV 186

- Laubry C Cottenot, P Routier D and Heim de Balsac III *Radiologie clinique du Coeur et des gros vaisseaux* Masson et Cie Paris 1939
- Liljestrand G Lysholm E Nylin G and Zachrisson C G "The Normal Heart Volume in Man" *Am Heart J* 1939 XVII 406
- McGinn E and White D D "Epicardial Fat Its Nonrecognition a Common Cause of Error in X ray Measurement of Heart Size" *JAMA* 1936 CVII 200
- Mazer M "A Simple Method for Measuring Cardiac Area from the Orthodiagram" *Am Heart J* 1942 XXIV 511
- Moritz F "Ueber orthodiagraphische Untersuchungen am Herzen" *Munch med Wchnschr* 1902 XLIX, 1
- Palmer J H "The Development of Cardiac Enlargement in Disease of the Heart A Radiological Study" *Medical Research Council Special Report Series No 277* His Majesty's Stationery Office London 1937
- Palmeri G G "La radioplastique du coeur" *Arch d mal d coeur* 1921 XIV 440
- Parkinson J and Bedford D E "The Aortic Triangle A Radiological Landmark in the Left (or II) Oblique Position" *Lancet* 1936 II 909
- Pezzi, C "The Radioscopic Sign of the Hilum Dance Its Clinical Significance" *Libman Anniversary Volumes* 1932 III 931
- Reynolds R J "Some Experiments on the Production of Rapid Serial Roentgenograms from the Screen Image by Means of a Cinematographic Camera" *Brit J Radiol* 1927 XXIII 33 and *Am J Roentgenol* 1928 XIX 469
- Cineradiography *Brit J Radiol* 1934 VII 415 and *Am J Roentgenol* 1935 XXXIII 522
- Robb D P and Steinberg I "Practical Methods of Visualization of Chambers of the Heart the Pulmonary Circulation and the Great Blood Vessels in Man" *J Clin Investigation* 1938 XVII 507 *Am J Roentgenol* 1939 XLI 1 and *JAMA* 1940 CXIV 474
- Roesler H "Relation of Shape of Heart to Shape of Chest With Special Reference to Anteroposterior Dimension and Morphology of Various Normal Heart Types Contribution to Question of Accuracy of Ordinary Roentgenological Methods of Heart Measurement" *Am J Roentgenol* 1934 XXXII 464
- Clinical Roentgenology of the Cardiovascular System*; Charles C Thomas Publisher Springfield Ill 2nd ed 1943 (1st ed 1937)
- Rohrer F "Volumbestimmung von Koerperhoelen und Organen auf orthodiagraphischem Wege" *Fortschr a d Geb d Rontgenstrahlen* 1916-17 XXIV 285
- Montgen, W K. "Ueber eine neue Art von Strahlen" *Verhandl d physik med Gesellsch Wurzburg*, 1895 NF XXIX, 132
- Sabat R "Ueber ein Verfahren der roentgenographischen Darstellung der Bewegungen innerer Organe (des Herzens der Aorta des Zwerchfells)" *Fortschr a d Geb d Rontgenst* 1913 XX 47
- Smith, H W and Bloedorn W A "The Size of the Normal Heart a Teleroentgen Study" *U S Naval M Bull* 1922 XVI 219
- Sosman M C "Technic for Locating and Identifying Pericardial and Intracardiac Calcifications" *Am J Roentgenol* 1943 L 461
- Spillane J D "Volumetric Reconstruction of the Heart in Health and in Disease A Radiological Study" *Brit Heart J* 1939 I 333
- Strandquist, M "Direction Indicator for Roentgen Tubes" *Acta radiol* 1935 XVI 304
- Stumpf P "Archiv und Atlas der normalen und pathologischen Anatomie in typischen Rontgenbildern Das roentgenographische Bewegungsbild und seine Anwendung (Flachenkymographie und kymoskopie)" *Fortschr a d Geb d Rontgenstrahlen* Ergaenzungsband 41 Georg Thieme Leipzig 1931
- Ungerleider H E and Gubner R "Evaluation of Heart Size Measurements" *Am Heart J* 1942 XXIV 494
- Valsalva A *De aure humana tractatus in quo integra auris fabrica multis novis inventis et iconibus illustrata describitur omniumque ejus partium uses indagantur Quibus interposita est musculorum uvulae atque pharyngis nova descriptio et delineatio* Tray ad Rhenum G vande Water 1717
- Vaquez, H and Bordet E *Radiologie du Coeur et des vaisseaux de la Base* J B Bailiere et Fils Paris 4th ed 1928



- Williams F H A Method for More Fully Determining the Outline of the Heart by Means of the Fluoroscope together with Other Uses of This Instrument in Medicine *Boston M and S J* 1896 CXXXV 335
- Zdansky E Beitrage zur Kenntnis der kardialen Lungenstauung auf Grund roentgenologischer klinischer und anatomischer Untersuchungen *Wien Arch f inn Med* 19.9 XVIII 461
- Letter *JAMA* 1936 CVI 227
- Röntgendiagnostik des Herzens und der grossen Gefasse* Julius Springer Wm. 1939

### Recent References (1944-1950)

- Axen O and Lind J "Table for Routine Angiocardiography Synchronous Serial Roentgenography in Two Planes at Right Angles" *JAMA* 1950 CXLIII 540
- Boone B R Gillick F G Chamberlain W E and Oppenheimer M J Electrokymograms of Heart Border Motion Principles of Record Interpretation *Federation Proc Fed of Am Soc for Exper Biol* 1946 V 2
- Bustamente R Perez Stable E Guerra III and Milanés II Visualización radiológica de las arterias coronarias *Arch del Inst de cardiol de Mex* 1950 XX 350
- Campbell M and Gardner F Radiological Features of Enlarged Bronchial Arteries *Brit Heart J* 1951 XII 183
- Castellanos A and Peretras R Retrograde or Counter Current Aortography *Am J Roentgenol* 1950 LXIII 559
- Castellanos A Pereiras R and Garcia O Angio-cardiografia en el niño *Arch de Med Infantil Habana* 1950 XIX 29
- Chavez I Dorbecker N and Celis A Direct Intracardiac Angiocardiography—Its Diagnostic Value *Am Heart J* 1947 XXXIII 560
- Dotter C T and Steinberg M B "Angiocardiographic Interpretation" *Radiology* 1949 LIII 513
- Hanson M E Nyare erfarenheter med aortografi" *Nord med* 1949 XLI 55
- Henny G C and Boone B R Electrokymograph for Recording Heart Motion Utilizing the Roentgenoscope *Am J Roentgenol* 1945 LIV 217
- Luisada A A Fleischner F G and Rappaport M II Fluorocardiography (Electrokymography) I Technical Aspects *Am Heart J* 1948 XXXV 336
- McAllister F F and Beck C S A New X ray Technic for Visualization of the Heart and Great Vessels" *Circulation* 1950 I 1049
- Meneses Hoyos J and Gomez del Campo C Angiographie de l'aorte thoracique par ponction directe *Cardiologia* 1951 XVIII 156
- Meyer R E A Method for Measuring Children's Hearts *Radiology* 1949 LIII 363
- Prinzmetal M Corday E Bergman H C Schwartz L and Spritzler R J "Radiocardiography A New Method for Studying the Blood Flow Through the Chambers of the Heart in Human Beings" *Science* 1948 CVIII 340
- Ponsdomenech E R and Nunez V B "Heart Puncture in Man for Diodrast Visualization of the Ventricular Chambers and Great Arteries (I) Its Experimental and Anatomophysiological Basis and Its Technique and Heart Puncture (II) Cardiac angiography Clinical and Electrocadiographic Results" *Am Heart J* 1951 XL 643 and 855
- Rushmer R F Cardiac Cinefluorography as a Training Method Abstract Program of 27nd Scientific Sessions *Am Heart A* 1949 p 44

---

## CHAPTER 8

---

# THE PULSATION OF HEART AND BLOOD VESSELS SPHYGMOGRAPHY BALLISTOCARDIOGRAPHY THE CAPILLARY CIRCULATION

Very little revision of this chapter has been needed for the present edition of this book. A brief section however has been added on ballistocardiography for it is here that such mechanical recording belongs.

---

Harvey W. *Exercitatio Anatomica De Motu Cordis Et Sanguinis In Animalibus*  
Frankfurt am Main 1628 (*An Anatomical Disquisition on the Motion of the  
Heart and Blood in Animals* Translation by Robert Willis for the Sydenham  
Society in 1847.)

### Chapter 1 The Author's Motives for Writing

"When I first gave my mind to vivisections as a means of discovering the motions and uses of the heart and sought to discover these from actual inspection and not from the writings of others I found the task so truly arduous so full of difficulties that I was almost tempted to think with Fracastorius that the motion of the heart was only to be comprehended by God. For I could neither rightly perceive at first when the systole and when the diastole took place nor when and where dilatation and contraction occurred by reason of the rapidity of the motion which in many animals is accomplished in the twinkling of an eye coming and going like a flash of lightning so that the systole presented itself to me now from this point now from that the diastole the same and then everything was reversed the motions occurring, as it seemed variously and confusedly together. My mind was therefore greatly unsettled nor did I know what I should myself conclude nor what believe from others. I was not surprised that Andreas Laurentius should have said that the motion of the heart was as perplexing as the flux and reflux of Euripus had appeared to Aristotle.

"At length and by using greater and daily diligence having frequent recourse to vivisections employing a variety of animals for the purpose and collating numerous observations I thought that I had attained to the truth that I should extricate myself and escape from this labyrinth and that I had discovered what I so much desired both the motion and the use of the heart and arteries since which

- Williams F H "A Method for More Fully Determining the Outline of the Heart by Means of the Fluoroscope together with Other Uses of This Instrument in Medicine" *Boston M and S J* 1896 CXXXV 335
- Zdansky E "Beiträge zur Kenntnis der kardialen Lungenstauung auf Grund roentgenologischer klinischer und anatomischer Untersuchungen" *Wien Arch f inn Med* 1909 XVIII 461
- Letter *JAMA* 1936 CVI 227
- Röntgendiagnostik des Herzens und der grossen Gefässe* Julius Springer Wm 1939

### Recent References (1944-1950)

- Axen O and Lind J "Table for Routine Angiocardiography Synchronous Serial Roentgenography in Two Planes at Right Angles" *JAMA* 1950 CXLIII 540
- Boone W H Gillick F G Chamberlain W E and Oppenheimer M J "Electrolymograms of Heart Border Motion Principles of Record Interpretation" *Federation Proc Fed of Am Soc for Exper Biol* 1946 V 9
- Bustamante R Perez Stable E Guerra R and Milanés B "Visualización radiológica de las arterias coronarias" *Arch del Inst de cardiología de Mex* 1950 XX 350
- Campbell M and Gardner F "Radiological Features of Enlarged Bronchial Arteries" *Brit Heart J* 1951 XII 183
- Castellanos A and Pereiras R "Retrograde or Counter-Current Aortography" *Am J Roentgenol* 1950 LXIII 559
- Castellanos A Pereiras R and García O "Angio-cardiografía en el niño" *Arch de Med Infantil Habana* 1950 XIX 29
- Chavez I Dorbecker N and Celis A "Direct Intracardiac Angiocardiography—Its Diagnostic Value" *Am Heart J* 1947 XXXIII 560
- Dotter C T and Steinberg M B "Angiocardiographic Interpretation" *Radiol of St* 1949 LIII 513
- Hanson H E "Nyare erfarenheter med aortografi" *Nord med* 1949 VLI 517
- Henny G C and Boone B R "Electrolymograph for Recording Heart Motion Utilizing the Roentgenoscope" *Am J Roentgenol* 1945 LIV 217
- Luisada A A Fleischner F G and Rappaport M B "Fluorocardiography (Electrolymography) I Technical Aspects" *Am Heart J* 1948 XXXV 336
- McAllister F F and Beck C S "A New X-ray Technique for Visualization of the Heart and Great Vessels" *Circulation* 1950 I 1049
- Meneses Hoyos J and Gomez del Campo C "Angiographie de laorte thoracique par ponction directe" *Cardiologia* 1951 XVIII 156
- Meyer R R "A Method for Measuring Children's Hearts" *Radiology* 1949 LIII 367
- Prinzmetal M Corday H Bergman H C Schwartz L and Spritzler R J "Radiocardiography A New Method for Studying the Blood Flow Through the Chambers of the Heart in Human Beings" *Science* 1948 CVIII 340
- Pon domenech E R and Nunez V B "Heart Puncture in Man for Diodrast Visualization of the Ventricular Chambers and Great Arteries (I) Its Experimental and Anatomophysiological Basis and Its Technique and Heart Puncture (II) Cardiac angiography Clinical and Electrocardiographic Results" *Am Heart J* 1951 VLI 643 and 855
- Rushmer R F "Cardiac Cinefluorography as a Training Method" Abstract Program of 22nd Scientific Sessions *Am Heart A* 1949 p 44

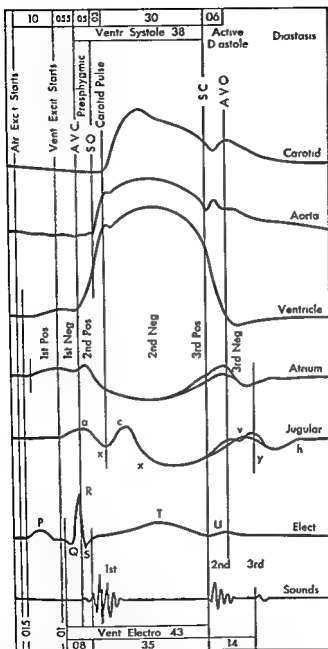


FIG 30 Chart showing time relations of electrocardiogram atrial and ventricular contractions pressure changes and heart sounds (Lewis *Mechanism and Graphic Registration of the Heart Beat* Kindness of Shaw and Sons Ltd London )

ence to the centre than in the opposite direction were there even no valves to oppose its motion

Sphygmography (*σφινγμος* pulse and *γραφειν* to write) is the process of obtaining a tracing of cardiovascular pulsation whether from the apex or pulse of the heart (*cardiogram*) from brachial radial or other artery (*arteriogram*) from jugular or other vein (*phlebogram*) or from pulsating liver (*hepatogram*). The term polygram applies to simultaneous records of any two or more pulses or of pulse and respiration. Commonly the polygram registers the brachial or radial pulse and the jugular pulse in addition the electrocardiogram is usually recorded simultaneously or even replaces one of the other mechanical graphic tracings. The instrument which makes any of these combined tracings is called the polygraph. The technic of sphygmography will not be discussed in this edition it is amply presented elsewhere (see Bibliography at end of this chapter). It need only be added here that developments in the last few years have made it possible to obtain with ease excellent electrical (galvanometric) tracings of cardiac arterial and venous pulses (Miller and White 1941) that total cardiac vibrations recorded by the cathode ray are now available for study (Kountz and Smith 1941) and that graphic records of the recoil of the body from the ejection of blood by the heart into the aorta (ballistocardiograms) have been utilized to estimate the cardiac output per beat (Starr et al 1939 1940).

### CARDIOGRAM

Although it may seem at first thought that records of the pulsation of the heart itself transmitted to the chest wall should be simple and reliable evidence for the analysis of the mechanism of the heart beat experience has shown otherwise. The result is that the cardiogram is rarely obtained or studied except in special instances or in investigative work. The reasons for this neglect are several. In the first place the technic is often far from easy. A thick chest wall pulmonary emphysema or very weak heart action may make it difficult or impossible to find any cardiac impulse at all. In the second place the shape and interpretation of the tracing depend on what part of the impulse is recorded whether that over the left ventricle at the apex or that nearer the sternum over the right ventricle. In the third place the complexity of the tracing which is often difficult to explain makes it less convenient than the arteriogram phlebogram and electrocardiogram in the analysis of arrhythmias. And finally in our present state of knowledge at least more helpful information is afforded us by the other tracings for example slight pulsus alternans in the arteriogram shown poorly or not at all in the cardiogram delay in atrio-ventricular conduction in the jugular phlebogram found with difficulty by direct cardiography and information about the myocardium shown by intra-ventricular block and T wave changes of the electrocardiogram and usually not even suggested by the cardiac apex tracing. Nevertheless the cardiogram is of some individual interest for itself and should be briefly described

The normal cardiogram varies according to whether it is obtained over left ventricle or right ventricle (Figure 31). Over the left ventricle the outthrusts and hence the upstrokes of the tracing occur with systole over the right ventricle unless it is enlarged systole causes depression. If the atrial contraction is vigorous and tracing conditions favorable we may find a definite upstroke preceding the sharp higher ventricular upstroke of the left ventricular apex impulse or preceding in the same way the sharp ventricular downstroke over the right ventricle. This a wave is more prominent over the right ventricle than over the left especially in the epigastrium. A record taken where systolic outthrust and retraction merge will show various and sometimes confusing combinations of the two tracing shapes. The wave due to ventricular contraction is usually overshoot in the tracing partly because of the actual event but also because of the varying degrees of inertia of the apparatus employed. Then follows during ventricular systole a settling down to a variable level till the shock of closure of aortic and pulmonary valves ends systole and begins diastole. Quite early in diastole (about a tenth of a second after its onset) there may appear coincident with a protodiastolic heart sound a slight impulse due probably to the vibration of the ventricular walls from the current of blood that enters at that time (Figure 31). Such a diastolic event is more likely to be recorded with forceful slow heart action in thin young persons or with serious protodiastolic gallop rhythm (discussed in Chapter 5). Finally various oscillations may appear in the cardiogram which are unexplained but are probably due to vibrations of the chest wall.

Abnormalities of the cardiogram include increased and decreased force and excursion of the atrial and ventricular systolic impulses and retractions, delay between these impulses in heart block and extra waves in gallop rhythm (see Figure 31).

Gross pulsatory movements of the wall of the thorax resulting from the heartbeat (Dressler 1937) have already been referred to in Chapter 5 page 69.

### ARTERIOGRAM PULSE WAVE VELOCITY

**Arteriogram** An arterial pulse tracing may be obtained from almost any superficial artery but it is customary to use the brachial or radial artery for such a purpose. Nearly a century ago the first attempts were made to study the circulation in man in health and disease by tracings on smoked paper made by crude instruments attached to the radial artery (Vierordt 1855 Marey 1860). Despite great expectations and extravagant interpretations the new records at first added little knowledge beyond that which had already been gained by mere palpation or inspection of the arterial pulse. As a result sphygmography was abandoned for nearly half a century except for special studies. The technic and apparatus poor and difficult at first slowly improved due to these special studies until with new discoveries concerning cardiac arrhythmia and alternation of the pulse the method was reintroduced into the clinic toward the end of the last century with far more success than at first.

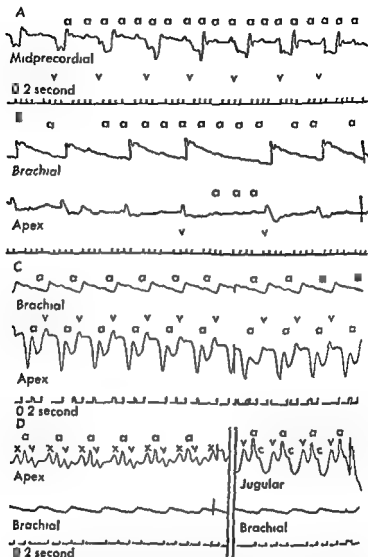


FIG 31 Cardiograms showing (A) ventricular systolic negative (v) and atrial systolic positive (a) waves in a case of complete heart block with the receiver placed over the precordium midway between the apex impulse and the lower end of the sternum and hence over the right ventricle (B) upstrokes with ventricular systole (v) and atrial systole (a) in the same case of complete heart block represented in (A) but with the receiver at the cardiac apex and hence over the left ventricle—note also the "a" waves in the brachial arteriogram taken simultaneously with the cardiogram (C) atrial (a) and ventricular (v) upstrokes with the receiver at the cardiac apex in a case with slight delay in a v conduction unusually vigorous atrial action and presystolic gallop rhythm and (D) three waves a v and x representing atrial ventricular and protodiastolic impulses with the receiver at the apex in a case of congestive failure showing well marked protodiastolic gallop rhythm without any delay in a v conduction (as proved by jugular phlebogram and electrocardiogram) Time interval = 0.2 second

It was almost entirely the shape and amplitude of the tracings that had attracted attention at the beginning rate and rhythm being largely ignored until many years later. The various shapes of tracings of the arterial pulse were prominent in the textbooks of the day and it was hoped that they might prove more useful than they did. We realize now that the shape and amplitude of the arteriogram are complicated not only in themselves but frequently also by the addition of artifacts due to the graphic method itself. By the employment of more accurate apparatus the distortion can now be avoided.

*The normal arterial pulse wave* The arteriogram consists of a graphic record of a series of pulse waves in an artery. It should be of normal rhythm and rate (40 to 100 per minute at rest usually 60 to 80). The normal pulse wave (Figure 32) shows at first a sharp upstroke rising a variable distance from the baseline, the amplitude depending on the fullness of the pulse and the sensitiveness of the recording apparatus. Vibrations may be found on the upstroke if the curve is taken by the use of the Frank capsule, crystal microphone and galvanometer or cathode ray; such vibrations are called anacrotic (ἀνα up and κροτο stroke). The upstroke is quickly succeeded by a short sharp fall to a notch called the predicrotic (πρὸ before δισ second and κροτο stroke) resulting from the artifact of overshooting or fling due to instrumental inertia. The distance from the peak of the wave to the predicrotic notch varies according to two factors: the amount of inertia of the recording apparatus and the fullness of the pulse; the more of each of these, the greater the distance. It is not always possible to make out this notch; it may be buried in the rapid decline to the dicrotic notch, especially where there is a water hammer or hyperdicrotic pulse shape. Following the predicrotic notch appears the curved systolic decline, ending as a rule abruptly at the dicrotic notch, which represents the time of aortic valve closure and second heart sound. The time interval from beginning of the main upstroke to the dicrotic notch (usually 0.25 to 0.35 second depending on the pulse rate) represents the duration of systole minus the so-called presphygmie (πρὸ before and σφύγμος pulse) interval, which is the time at the beginning of systole after the closure of the mitral and tricuspid valves (time of first sound) when intraventricular pressure is rising but not sufficiently to raise the aortic cusps and start the pulse wave along the aorta. This presphygmie interval or isometric (ἴσος equal and μέτρον measure) phase is very short (calculated variously as 0.04 to 0.08 second). The dicrotic notch is followed by the dicrotic wave, usually a slight convexity upward due to the rebound of the pulse wave at the closure of the aortic cusps. This gives way to a gradual fall of the baseline to the next systolic upstroke. Rarely a very small additional wave (α) occurs just preceding the systolic upstroke due to the effect of atrial systole on intraventricular and aortic pressure. Finally, when more accurate tracings are obtained, as already mentioned, additional oscillations, for example on the systolic upstroke, may be seen doubtless due to vibrations of the artery wall; their recording is not of any practical significance in the present state of our knowledge but may perhaps be found to be of some importance by future studies.



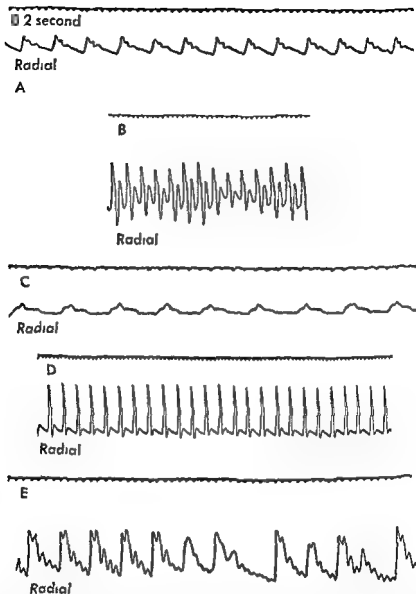


FIG. 32 : Arteriograms showing various shapes of pulse curves with normal rhythm (A) Normal average shape of arterial pulse wave showing upstroke predicrotic notch (due to artifact of overshooting from inertia of instrument) and dicrotic notch and wave (due to closure of aortic valve)—the duration of systole is equivalent to the interval from the beginning of the upstroke to the dicrotic notch plus a small time interval representing the presphygmic period (see text) (B) Hyperdicrotic pulse in infection showing exaggeration of the dicrotic notch and wave (C) Plateau and anacrotic pulse of aortic stenosis (D) Water hammer pulse of aortic regurgitation (E) Deformity of radial arteriogram due to oscillations caused by paralysis agitans. Note also two ventricular premature beats. Time interval of these and succeeding arteriograms and polygrams = 2 second

*Abnormalities of the arterial pulse wave in shape and amplitude* Slight changes in shape and amplitude of the arterial pulse wave from the average normal are so generally found in arteriograms or are so easily caused by the procedure of registration itself that only well marked variations such as can be palpated in the radial pulse should be considered here. Great increase in pulse pressure that is true increase in artery fullness is not always easily apparent either on palpation of the arterial pulse or in the arteriogram. Its detection is dependent on relative emptiness of the artery in diastole along with increase of pulse pressure but the diastolic laxness of the vessel is more essential than is increase in pulse pressure.

Various abnormalities of shape and amplitude found in the arteriogram are illustrated in Figures 32 and 33.

The most important by far of these abnormalities is *pulsus alternans* which consists of alternating fullness of pulse and of systolic and pulse pressure during normal heart rhythm the result of weakness (generally serious) of the left ventricle (see Chapter 30). An interesting variation abnormal and diagnostic (usually of acute or chronic constrictive pericarditis) when of high degree is the *pulsus paradoxus* which consists of waxing and waning of the pulse volume (and pressure) with expiration and inspiration respectively in contrast to the usual increase of the pulse fullness during inspiration and its decrease during expiration in the case of normal diaphragmatic breathing in marked instances the radial pulse may entirely disappear during inspiration (see Chapters 6 and 27). The various arrhythmias will not be illustrated here because they are so much better shown in electrocardiograms (see Chapters 32, 33 and 34).

*Velocity of the arterial pulse wave* Quite aside from form and rhythm of the pulse and speed and volume of blood flow is the measurement of the velocity of the arterial pulse wave. This has been estimated in various ways most simply by measuring the time interval between the appearances of the carotid and radial pulse waves graphically recorded simultaneously and dividing this time interval into the difference in centimeters between the distances from the heart of the recording points on the two arteries. This gives roughly the speed of travel of the pulse wave in centimeters per second. More accurate methods for making this measurement have been in recent years introduced such as that of the use of the hot wire sphygmograph which is an instrument transforming into variations of an electric current recorded by galvanometer the air pressure waves transmitted from a pulsating vessel or from the heart through a tube past a fine spiral of platinum wire heated by the electric current whose variations are recorded the ends of this wire being connected with the galvanometer. Normally the pulse wave velocity in the brachial and radial arteries has been found to be 5 to 9 meters per second averaging about 7 meters. It is increased in hypertension and arteriosclerosis and decreased in hypotension aortic stenosis and aortic aneurysm. It varies roughly with the speed of blood flow but it has little or no relation

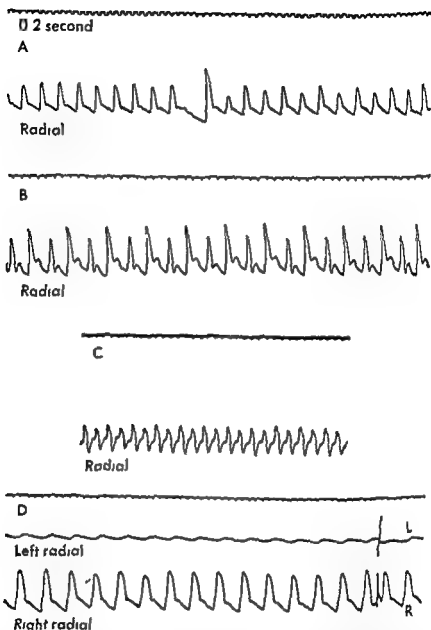


FIG 33 Arteriograms showing pulsus alternans and unilateral pulse deformity due to aneurysmal obstruction (A) Ventricular premature beat with compensatory pause followed by slight to moderate alternation of the pulse (B) Constant pulsus alternans showing delay in appearance of alternate weak beats (C) Pulsus alternans during a paroxysm of tachycardia (rate 185 per minute) (D) Diminished and delayed left radial pulse waves due to aortic aneurysm with obstruction at the mouth of the left subclavian artery

to volume of blood flow The measurement of the velocity of the pulse wave is not of much clinical value

### PHLEBOGRAM HEPATOGRAM

**Phlebogram** (φλεψ vein and *γραμα* inscription) The phlebogram or graphic record of the venous pulse is routinely obtained from the jugular vein Although on rare occasions pulsations may be easily visible in other superficial veins as in the arms the jugulars as a rule are the only veins that show enough pulsation to give a satisfactory record this is due to their large size and close proximity to the heart Venous pulsation has been known for centuries but it was not until the latter half of the last century that the development of the sphygmograph permitted the taking of actual tracings (Friedreich 1866 Potain 1867) and serious study of these venous pulse tracings did not begin until stimulated by a curiosity concerning the clinical significance of variations of this pulse (Mackenzie 1893) Gradually by comparing the phlebogram thus obtained with cardiac or arterial pulse tracings it became possible to recognize although not completely to explain the various waves of the normal jugular pulse and to describe certain abnormalities

In the clinic for a while the analysis of disturbances of the cardiac mechanism like partial heart block was chiefly dependent on the study of the polygram which consisted of simultaneous jugular and arterial pulse tracings But the frequently difficult and bothersome technic and the obscurity concerning interpretation in the minds of most physicians prevented a wide adoption of the method doctors remaining content to continue for years the old custom of labeling irregularity of the heart rhythm as slight moderate or marked Eventually the interest of younger workers and especially the introduction of the practical electrocardiograph the string galvanometer into the field of internal medicine resulted in the clinical applications of the lessons about cardiac mechanism first studied in the phlebogram by pioneers The electrocardiogram gives information about the cardiac mechanism which is so much more accurate and complete than that given by the phlebogram and the technic of securing the electrocardiogram and its interpretation when obtained are both so much easier that the phlebogram has been almost completely abandoned However as in the case of the arteriogram help can still sometimes come from the phlebogram To represent graphically what one can see of jugular pulsation aids in understanding the mechanical evidences of cardiac action and is good training Also in certain cases when the electrocardiogram is not available and one deals with arrhythmias difficult to analyze without knowing how the atria are acting the phlebogram may solve the problem And even when an electrocardiogram has been secured the question as to whether atrial waves are isoelectric or buried in ventricular waves may be answered by a study of the phlebogram The jugular pulse tracing gives something the electrocardiogram cannot give that is mechan-

cal evidence of action of the heart chambers moreover certain abnormalities of the jugular pulsation may reveal cardiac insufficiency even when the electrocardiogram is normal In addition one can by electrical recording now obtain phlebograms with greater ease and accuracy than was possible in the past (Miller and White 1941)

*The normal and abnormal jugular phlebogram* Although proof does not exist for every detail of the interpretation of the normal jugular pulse tracing the phlebogram is understood sufficiently to permit fairly full analysis With each cardiac cycle there are normally three four five or even six waves in the jugular pulse Interpretation by inspection of these waves especially if there are more than three may prove to be very confusing Therefore although it is at times possible to see and to identify the three normal waves or in the case of abnormalities to make correct analyses there are so many variations that in spite of much experience interpretation by inspection of the vein is far less reliable than interpretation of the phlebogram itself

There are three main waves in the jugular pulse (Figure 34)

The first wave due to atrial systole, has been routinely called the *a* wave It can be identified only indirectly after the other two main waves (which are of ventricular origin) have been accurately measured off as a rule it precedes the second or *c* (ventricular systolic) wave by one fifth of a second and it is variable in size depending chiefly on the posture of the subject the force of the atrial contraction and the degree of dilatation of the jugular vein Other factors which influence the size of the *a* wave normally are instrumental technic and the fullness of blood flow With poor technic for example by the application of too much pressure so that the vein is nearly collapsed or by holding the receiver somewhat away from the optimum position the *a* wave of the phlebogram may be small and poorly defined With increased heart action the *a* usually increases in amplitude and with increased circulation associated with increased blood volume such as may temporarily result from the ingestion of a large amount of fluid the *a* wave may also increase in size It is biggest of all in cases of marked tricuspid stenosis with normal rhythm It is ordinarily a single wave a rounded upstroke rising sometimes at the peak of the jugular pulse sometimes low near the baseline and sometimes at midlevel its position depending on the speed of the pulse on the degree of stasis in the vein and on the relative submergence of the *a* in the ventricular systolic wave The slower the pulse or the more congested the vein the more the *a* wave tends to appear at the top of the curve The faster the pulse the less the congestion and especially the more the systole of the ventricles is emphasized in the tracing the lower lies the *a* wave Although the *a* wave appears normally to be a single wave this appearance may be in part due to the immediate succession of the ventricular systolic wave which conceals any other portion of the *a* wave When there is a delay in atrioventricular conduction partial or complete sufficient to separate clearly atrial and ventricular waves the *a* wave sometimes appears doubled

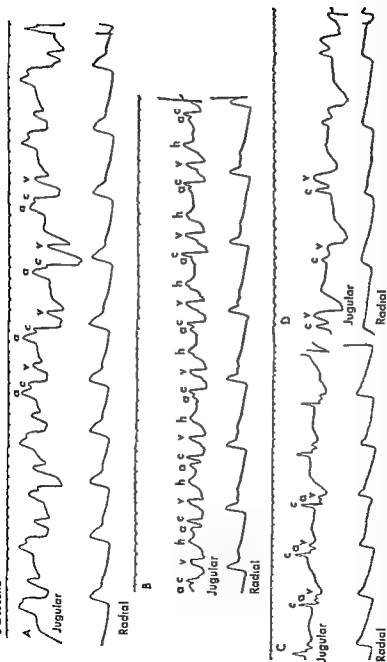


FIG 34 Polygrams showing the jugular phlebogram in (A) normal sinus arrhythmia (a = atrial c = ventricular and v = stasis waves) (B) sinoatrial bradycardia with h waves (see text) in addition to the a c and v waves (C) atrioventricular nodal rhythm in which the atrial contraction follows the ventricular as shown by the interpolation of the a wave between the c and v waves and (D) atrial standstill in which condition no a waves are seen either between or with the regularly recurring c and v waves

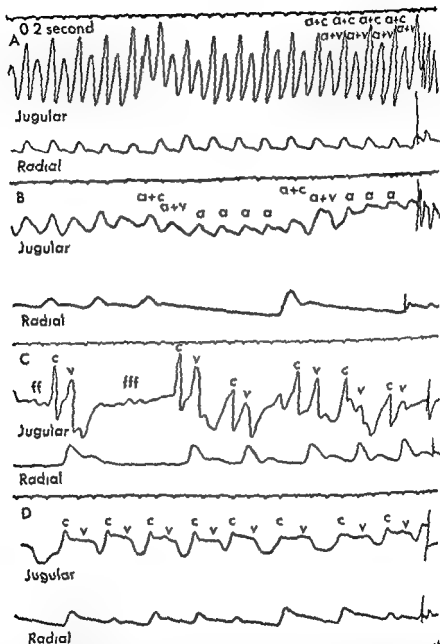


FIG 35 Polygrams showing the jugular phlebogram in (A) atrial flutter with two to one a-v block ( $a$  = atrial  $c$  = ventricular and  $v$  = stasis waves) (B) atrial flutter with varying and higher degrees of block the  $a$  waves being clearly evident between the  $c$  waves (C) atrial fibrillation with no  $a$  waves but with oscillations (fff) due to the irregular atrial contractions and (D) atrial fibrillation with the so-called "congestive" type of venous pulse due to coalescence of  $c$  and  $v$  waves resulting from stasis

or at least notched (Figure 36) Various abnormalities of the jugular phlebogram are illustrated in Figures 34 35 and 36 Arrhythmias are not presented because of their better analysis by electrocardiography (Chapters 32 33 and 34) except as they illustrate particular points concerning the venous pulse tracing

*The a-c interval* The atrial wave of the jugular pulse tracing precedes normally that due to ventricular systole by 0.15 to 0.20 second if there is a greater time interval (measured from the beginning of the *a* upstroke to the beginning of the *c* upstroke) atrioventricular block is present

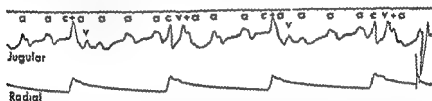


FIG 36 Polygram showing the jugular phlebogram in complete atrioventricular block with complete dissociation of *a* and *c* waves Note brief *a* waves Size reduced

Following the first or *a* wave of the normal jugular phlebogram by the time interval just noted above appears the second or *c* wave which is due to ventricular systole It was labeled *c* because it was attributed to the pulsation of the carotid artery lying under the jugular vein Undoubtedly the carotid pulsation does play an important part in its production but this part is variable in degree In the venous pulsation itself there is a ventricular systolic wave transmitted up from the right atrium by way of the superior vena cava This wave together with that due to the carotid pulsation forms the upstroke *c* of the jugular phlebogram a positive wave of varying amplitude whose size depends upon a number of factors The greater the carotid element of the *c* wave the higher and more preponderant is this wave and vice versa There is one type of patient with mitral stenosis with greatly exaggerated *c* (and *v*) waves of the jugular pulse itself that deserves special mention This pulsation concerns the deep jugular veins on both sides of the neck but especially the right one Because as a rule atrial fibrillation is present in these patients with no *a* waves in the phlebogram because the pulse is so vigorous and because it is so deep in position in the neck it is easily and commonly confused with the carotid pulse (White and Cooke 1939) It is due to tricuspid regurgitation with relatively little constant congestion or stasis so that the pulse wave is propelled vigorously by right ventricular systole through tricuspid valve right atrium and superior vena cava into the jugular veins it is easily obliterated by slight pressure over the jugular bulb As a rule tricuspid valve deformity with stenosis is present in these cases of such pulsation of long standing but in rare instances there is chronic irreversible dilatation of the tricuspid ring without valve deformity

The *c* wave itself is identified by comparative measurement from the upstroke of the pulse wave of the brachial or radial arteriogram or of the *QRS*



wave of the electrocardiogram which is taken simultaneously with the jugular phlebogram for this very purpose. Measuring back from simultaneous time lines of both tracings established by allowing the pens each to write a stroke with the recording surface at rest the beginning of the upstroke of the *c* wave will be found one tenth of a second earlier than the upstroke of the radial pulse wave or 0.135 second later than the *QRS* wave this difference in time being that interval required for the pulse wave to travel a length of artery equivalent to the difference between the distances of the radial pulse and of the jugular pulse from the heart in the first instance and to the sum of the travel time from the heart to the jugular bulb and of the electrical pre-sphygmic interval in the second instance (see Figure 31 page 158).

The *c* wave may be found to occur irregularly rapidly or slowly and to be of varying shapes and amplitudes but these characteristics of the arterial pulse and of heart action are better studied in the arteriogram itself as already discussed or in the electrocardiogram.

The third main wave the *v* wave of the jugular phlebogram is due primarily to stasis that is to the gradual accumulation of blood in right atrium superior vena cava and jugular bulb at the close of ventricular systole. This stasis ends rather abruptly in a rounded peak and downstroke when diastole begins and the blood flows down into the right ventricle from atrium vena cava and jugular bulb. It has been called routinely the *v* wave for ventricular systole but a more correct expression might have been *s* for stasis while the *c* wave might better have been called the *v* wave. However the firm establishment and the partial correctness of these designations warrant their retention. A second factor besides stasis which has been suggested as in part responsible for the *v* wave is the rebound or return upward of the base of the heart at the beginning of diastole. We do not know the relative importance of the two elements (the rebound and the stasis) or whether the frequent splitting of the *v* wave which is unexplained can result from their difference in time (the diastolic rebound effect being later than the other) but evidence strongly supports the conclusion that stasis and not diastolic rebound is the essential cause of the *v* wave. The amplitude of the *v* wave varies as does that of the *c* wave and as a rule inversely as that of the *c* wave. It is dependent to an important degree on the amount of venous stasis. If there is much stasis the *v* wave is more prominent. If the stasis is extreme in degree there appears a characteristic variation consisting in a merging of *c* and *v* waves in one broad plateau with slight elevations at the ends and variable concavity between (Figure 35). This type of jugular pulse was once called the ventricular type apparently because it was so often found in atrial fibrillation with absence of *a* waves. But it may be found with normal rhythm and *a* waves. It is due to congestion and so it may better be called the congestive type of jugular pulse.

The *v* wave is determined in its position in the jugular phlebogram by correlation with the radial arteriogram simultaneously recorded. Measuring back from synchronous points we find that the dicrotic notch of the arterial

pulse coincides with the peak of the  $\nu$  wave though sometimes it may fall between the two peaks of the  $\nu$ . Actually the dicrotic notch of the radial pulse represents closure of the aortic valve an earlier event by 0.05 to 0.1 second than the opening of the tricuspid valve which is responsible for the beginning of the downstroke of the  $\nu$  wave. But since the pulse wave takes almost 0.1 second longer to reach the wrist (or slightly less time to reach the elbow) than to reach the base of the neck these two events can be measured off together in the polygram.

One further wave may be found infrequently in the jugular pulse tracing especially with slow forceful heart action. It is a small wave in diastole called the  $h$  or  $b$  wave (Hirschfelder 1907 Gibson 1907). It is related to the preceding ventricular systole and not to the succeeding  $a$  or  $c$  waves which it may closely approach in time if the pulse is fast. It has been ascribed to the same mechanism that produces the normal third sound of the heart or the abnormal extra sound in protodiastolic gallop rhythm but its timing sometimes appears late for this. It is not well understood further study is needed to explain it. Whatever its mechanism it does not at present appear important except that its existence should be recognized so that it will not be confused with other waves (Figure 34). The  $a$  and  $h$  waves are located by a process of exclusion after the  $c$  and  $\nu$  waves have been identified.

What has been termed a second stasis or second onflow wave is the gradual movement upward of the baseline of the jugular phlebogram late in diastole just prior to the  $a$  wave. It is prominent if there is bradycardia or congestion.

An interesting phenomenon which sometimes interferes with smooth recording of the jugular pulse is the paradoxical inspiratory filling in cases of venous hypertension (Hitzig 1942) this has been discussed in Chapter 6 page 120. It emphasizes the need well known to those experienced in phlebography to obtain for their smoothness records taken during held respiration that is held in whatever phase brings out the pulse waves to the best advantage.

An esophageal tracing of the left atrial pressure changes (esophagocardiogram) shows three waves usually corresponding to the  $a$ ,  $c$  and stasis waves of the jugular pulse tracing. The  $a$  and  $c$  waves may be inverted if the receiver (a capsule filled with air) lies directly over the left atrium for the atrium recedes when it contracts as does the left ventricle. This method however is an impracticable and unnecessary one.

**Hepatogram** ( $\eta\pi\alpha\rho$  liver and  $\gamma\rho\alpha\mu\mu\alpha$  inscription). A brief discussion of the liver pulse remains. A true perceptible liver pulse not due to directly transmitted systolic movement of the liver by heart, aorta or aneurysm is uncommon. The reason for this is that the liver is so sponge like that it absorbs much blood and much pulsation before it becomes sufficiently influenced actually to cause a visible palpable or traceable pulse. Slowly progressive chronic pericarditis or heart failure although resulting in much hepatic enlargement with some fibrotic change and ascites does not cause liver pulsation. Three factors are responsible for this pulsation (1) rapid acute congestion with failure and functional tricuspid regurgitation (2)

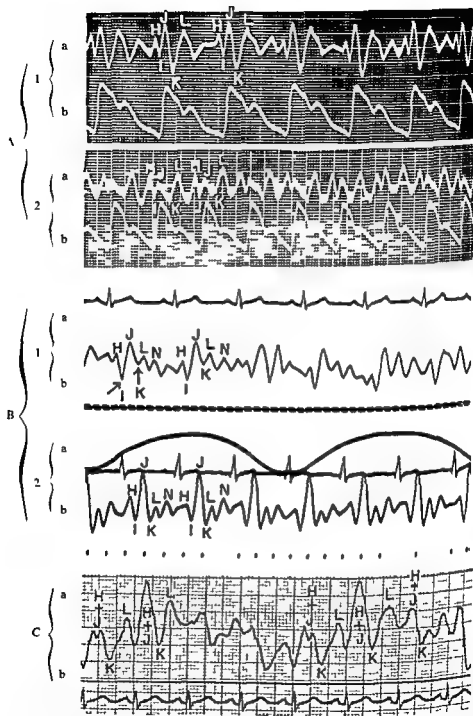


FIG 38 Ballistocardiograms (A 1) Normal curve Male age 34 Tracing shows normal waves H to K (period of cardiac ejection) Amplitude of J and K roughly approximate clinical measure of the stroke volume of the heart (a ballistocardiogram b arteriogram) (A 2) During acute rheumatic carditis The J and K waves are of

**Rheocardiogram** The changes that occur in the body's electrical resistance with each heartbeat can also be recorded electrically by connecting electrodes on right arm and left leg to alternating current of high frequency (10 000 to 50 000 oscillations per second) Measurement of electrical impedance of the body is not new in 1937 Mann stated "When the electrical conductivity of any part of the body is measured by means of an alternating current bridge it is found that this conductivity shows a rhythmic variation synchronous with the pulse The curve which has been called an electrical plethysmogram ascends with increase in body resistance during systole when the heart volume decreases relative to the lung air volumes on either side and descends when diastole begins In myocardial failure with prolongation of the isometric period the descent of the curve is delayed and with mitral regurgitation the ascent is slowed (Holzer and Polzer 1947) Complete inversion of the curves has been reported in cases with extensive edema with reversal when the edema cleared (Weissel 1948) This technic has not however been adopted routinely in clinical practice further investigation is needed even to determine whether or not it has any value as a research tool Recent work has indicated its possible value in the study of the peripheral circulation (Nyboer 1950) where it may act as an electrically recording plethysmograph

### CAPILLARY CIRCULATION AND PULSATION

It remained for Malpighi in 1661 to complete the proof of the circulation of the blood presented by Harvey in 1628 Harvey had postulated that "in the limbs and extreme parts of the body the blood passes either immediately by anastomosis from the arteries into the veins or mediately by the pores of the flesh, or in both ways as has already been said in speaking of the passage of the blood through the lungs Only in recent years has the existence of direct anastomoses between arteries and veins been demonstrated (Grant, 1931 Grant and Bland 1931) but the pores of the flesh or capillaries were discovered in the lungs by Malpighi.

Malpighi in a letter to Professor Alphonsus Borellius of Pisa describes his discovery of the pulmonary capillaries. (*De pulmonibus observationes anatomicae* Bologna 1661 translated by James Young M.D. *Proc Roy Soc Med* 1929-1930 XXIII 7-11 Part I)

low amplitude with relatively tall H and L waves (a ballistocardiogram b arteriogram) (Kindness of Dr William Dock, Brooklyn, N Y)

(B 1) Ballistocardiogram and electrocardiogram of case of coarctation of aorta before operation showing relatively small J wave and very small K wave The arrows point to the short J and K strokes characteristic of coarctation of the aorta (a electrocardiogram b ballistocardiogram) (B 2) Same case after operation the J and K waves are now normal (a electrocardiogram b ballistocardiogram) (Kindness of Dr Herbert R Brown, Jr., Rochester N Y., and *New England J Med*)

(C) Case of angina pectoris, A M male age 49 Note respiratory effects but in particular the fusion and/or notching of the H and J waves (a ballistocardiogram b electrocardiogram) (Kindness of Dr William Dock, Brooklyn, N Y)

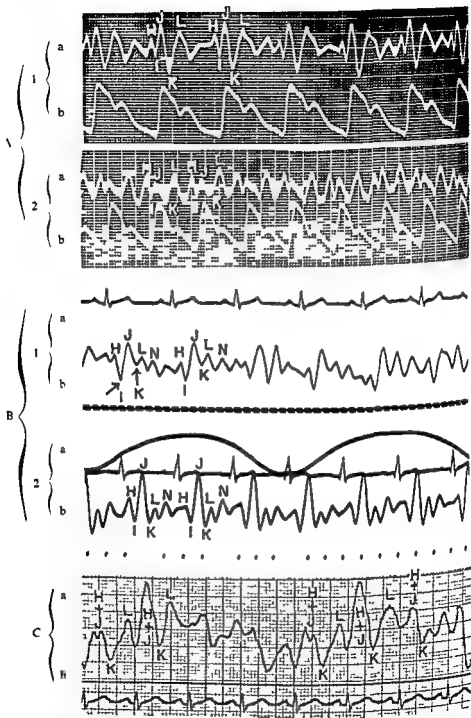


FIG 38 Ballistocardiograms (A 1) Normal curve Male age 34 Tracing shows normal waves H in K (period of cardiac ejection) Amplitude of J and K roughly approximate clinical measure of the stroke volume of the heart (a ballistocardiogram b arteriogram) (A 2) During acute rheumatic carditis The J and K waves are of

**Rheocardiogram** The changes that occur in the body's electrical resistance with each heartbeat can also be recorded electrically by connecting electrodes on right arm and left leg to alternating current of high frequency (10 000 50 000 oscillations per second) Measurement of electrical impedance of the body is not new in 1937 Mann stated When the electrical conductivity of any part of the body is measured by means of an alternating current bridge it is found that this conductivity shows a rhythmic variation synchronous with the pulse The curve which has been called an electrical plethysmogram ascends with increase in body resistance during systole when the heart volume decreases relative to the lung air volumes on either side and descends when diastole begins In myocardial failure with prolongation of the isometric period the descent of the curve is delayed and with mitral regurgitation the ascent is slowed (Holzer and Polzer 1947) Complete inversion of the curves has been reported in cases with extensive edema with reversal when the edema cleared (Weissel 1948) This technic has not however been adopted routinely in clinical practice further investigation is needed even to determine whether or not it has any value as a research tool Recent work has indicated its possible value in the study of the peripheral circulation (Nyboer 1950) where it may act as an electrically recording plethysmograph

### CAPILLARY CIRCULATION AND PULSATION

It remained for Malpighi in 1661 to complete the proof of the circulation of the blood presented by Harvey in 1628 Harvey had postulated that in the limbs and extreme parts of the body the blood passes either immediately by anastomosis from the arteries into the veins or mediately by the pores of the flesh or in both ways as has already been said in speaking of the passage of the blood through the lungs Only in recent years has the existence of direct anastomoses between arteries and veins been demonstrated (Grant 1931 Grant and Bland 1931) but the pores of the flesh or capillaries were discovered in the lungs by Malpighi

Malpighi in a letter to Professor Alphonsus Borellus of Pisa describes his discovery of the pulmonary capillaries (*De pulmombus observationes anatomicae* Bologna 1661 translated by James Young MD *Proc Roy Soc Med* 1929-1930 XXIII 7-11 Part 1)

low amplitude with relatively tall H and L waves (a ballistocardiogram b arteriogram) (kindness of Dr William Dock Brooklyn N Y)

(B 1) Ballistocardiogram and electrocardiogram of case of coarctation of aorta before operation showing relatively small J wave and very small K wave The arrows point to the short J and K strokes characteristic of coarctation of the aorta (a electrocardiogram b ballistocardiogram) (B 2) Same case after operation the J and K waves are now normal (a electrocardiogram b ballistocardiogram) (kindness of Dr Herbert R Brown Jr Rochester N Y and *New England J Med*)

(C) Case of angina pectoris AD male age 49 Note respiratory effects but in particular the fusion and/or notching of the H and J waves (a ballistocardiogram b electrocardiogram) (kindness of Dr William Dock Brooklyn N Y)

And now most famous man I will handle the matter more closely There were two things which in my epistle about observation on the lungs I left in doubtful and to be investigated with more exact study

(1) The first was what may be the network described therein where certain bladders and sinuses are bound together in a certain way in the lungs

(2) The other was whether the vessels of the lungs are connected by mutual anastomosis or gape into the common substance of the lungs and sinuses

The solution of these problems may prepare the way for greater things and will place the operations of Nature more clearly before the eyes For the unloosing of these knots I have destroyed almost the whole race of frogs which does not happen in that savage *Batrachomyomachia* of Homer For in the anatomy of frogs which by favour of my very excellent colleague D Carolo Fracassato I had set on foot in order to become more certain about the membranous substance of the lungs it happened to me to see such things that not undeservedly I can better make use of that (saying) of Homer for the present matter—

I see with my eyes a work trusty and great

For in this (frog anatomy) owing to the simplicity of the structure and the almost complete transparency of the vessels which admits the eye into the interior things are more clearly shown so that they will bring the light to other more obscure matters —

Observation by means of the microscope will reveal more wonderful things than those viewed in regard to mere structure and connection for while the heart is still beating the contrary (i.e. in opposite directions in the different vessels) movement of the blood is observed in the vessels—though with difficulty—so that the circulation of the blood is clearly exposed This is more clearly recognized in the mesentery and in the other greater veins contained in the abdomen

Thus by this impulse the blood is driven in very small (streams) through the arteries like a flood into the several cells one or other branch clearly passing through or ending there Thus the blood much divided puts off its red colour and carried round in a winding way is poured out on all sides till at length it may reach the walls the angles and the absorbing branches of the veins

The power of the eye could not be extended further in the opened living animal hence I had believed that this body of the blood breaks into the empty space and is collected again by a gaping vessel and by the structure of the walls The tortuous and diffused motion of the blood in divers directions and its union at a determinate place offered a handle to this But the dried lung of the frog made my belief dubious This lung had by chance preserved the redness of the blood in (what afterwards proved to be) the smallest vessels where by means of a more perfect lens no more there met the eye the points forming the skin called *Sagrino* but vessels mingled annularly And so great is the divarication of these vessels as they go out here from a vein there from an artery that order is no longer preserved but a network appears made up of the prolongations of both vessels This network occupies not only the whole floor but extends also to the walls and is attached to the outgoing vessel as I could see with greater difficulty but more abundantly in the oblong lung of a tortoise which is similarly membranous and transparent Here it was clear to sense that the blood flows away through the tortuous vessels that it is not poured into spaces but always works through tubules and is dispersed by the multiplex winding of the vessels —

Physiologic studies of the capillary circulation have in late years attracted much attention and have revealed new facts of some importance (Krogh Lewis Lombard Richards Crawford Landis) but in routine or even in special cardiovascular examination they have not yet proved important. The reasons for this are two. In the first place but few capillaries in man can be studied and these are at the body surface best seen at certain localities like the nail beds and subconjunctiva (and with difficulty in the eye grounds). In the second place great variations of capillary conditions exist not only throughout the body at a given moment but even in a single area at different moments due to the frequent periods of changing activity (dilatation) and rest (contraction) characteristic of arterioles and body capillaries in general. Thus capillary findings at a given moment in a given area may be very different from those in many other areas or in the same area at a different time. There are however certain clinical facts of interest determined by scrutiny of skin capillaries by microscope through the intervention of oil and the use of reflected light for illumination (Lombard 1912). In cyanotic states as in some cases of congenital heart disease with polycythemia or in one of the phases of Raynaud's disease capillaries of the fingers are widely dilated while the blood stream through them may be sluggish normal or rapid according to the state of the arterioles. In conditions of pallor as in another phase of Raynaud's disease the capillaries and arterioles are constricted and the blood stream is slowed. The ingenious studies by Crawford (1926 1927) and Landis (1930 1934 1938) have revealed interesting facts about the structure and action of the capillaries and concerning capillary blood pressure and permeability.

**Capillary pressure** Landis (1930 1934 1938) by microinjection measured directly and studied the mean blood pressure in the capillaries of the human skin at the base of the finger nail. He found the average pressure in the arteriolar limb of the capillary to be 32 mm of mercury at the end of the loop 20 mm and in the venous limb 12 mm. The fall of blood pressure does not cease at the junction of the arterioles and capillaries he wrote but continues unbroken through the capillary loop. Average blood pressure in the arteriolar limb is above and in the venous limb below the osmotic pressure of the plasma proteins. These direct pressure readings in human capillaries are in agreement with Starling's hypothesis of fluid balance. Landis further found that hyperemia due to heat was attended by a doubling of the capillary blood pressure. Eichna and his associates (1942 1943) have shown that despite the fact that pressure in the capillaries of the digits falls somewhat with arteriolar constriction and rises somewhat with increase in venous pressure there is a surprising degree of constancy in the digital capillary pressure during wide fluctuations in digital blood flow. Eichna (1943) reported his finding of the average digital capillary blood pressure in human fingers with intact innervation to be 18.5 mm of mercury in the arteriolar limb (summit 22.4) and 19 mm in the venous limb. Recently Pappenheimer and Soto



Rivera (1948) have further confirmed the concept that capillary pressure and colloid osmotic pressure are in balance by measuring the rate of filtration of fluid from blood to tissues and absorption of fluid from tissues to blood in the isolated hindlimbs of cats and dogs under conditions such that the arterial perfusion pressure the venous pressure and the protein osmotic pressure could be independently adjusted to desired constant values

**Capillary pulsation** Capillary pulsation can be recorded only photographically by cinematograph under high power magnification With low power magnification pulsation in the smaller arteries would be predominant Visible capillary pulsation is due to vasodilatation or marked aortic regurgitation allowing the arterial pulse to enter the capillaries without adequate damping The site of the color change is in the subpapillary venous plexus (Lewis 1927) This capillary or venular pulsation may be general throughout the body or very local

## BIBLIOGRAPHY

THE PULSATION OF HEART AND BLOOD VESSELS MECHANICAL RECORDS PULSE WAVE VELOCITY BALLISTOCARDIOGRAPHY CAPILLARY CIRCULATION AND PULSATION

SEE ALSO GENERAL REFERENCES FOLLOWING CHAPTER 2 AND IN PART IV  
DISORDERS OF CARDIOVASCULAR FUNCTION

- Bazett H C and Dreyer N H "Measurements of Pulse Wave Velocity" *Am J Physiol* 1924 LXIII 94
- Dressler W Pulsations of the Wall of the Chest *Arch Int Med* 1937 LX 437 441 654 and 663
- Ewing E M The Venous Pulse *Am J Physiol* 1914 XXXIII 159
- François Franck Mouvement des veines du cou en rapport avec l'action de la respiration et du coeur *Gaz hebdomadaire de médecine et de chirurgie* 1882 pp 132 156 225 and 255
- Frank O Dynamik der Membranmanometer und der Lufttransmission" *Ztschr f Biol* 1907-8 L 309
- Friedreich N Ueber den Venenpuls *Deutsch Arch f klin Med* 1866 I 441
- Gibson, A G The Significance of a Hitherto Undescribed Wave in the Jugular Pulse *Lancet* 1907 II 1380
- Harvey W *Exercitatio Anatomica De Motu Cordis Et Sanguinis in Animalibus* Frankfurt am Main 1628
- Hirschfelder A D "Some Variations in the Form of the Venous Pulse" *Bull Johns Hopkins Hosp* 1907 XVIII 265
- Hitzig W M On Mechanisms of Inspiratory Filling of the Cervical Veins and Pulsus Paradoxus in Venous Hypertension *J Mt Sinai Hosp* 1942 VIII 625
- Holzer W and Polzer K Rheokardiographie ein neues Kreislaufuntersuchungsverfahren *Schweiz med Wchnschr* 1947 LXXVII 921
- Kountz, W B and Smith J B "Total Cardiac Vibrations Recorded by the Cathode Ray" *Soc Proc J Clin Investigation* 1941 XX 458
- Lancisi G M *De Motu Cordis et Aneurysmatibus* Rome 1728
- Lewis T *The Mechanism and Graphic Registration of the Heart Beat* Shaw & Sons Ltd London 3rd ed 1925 (1st ed 1911)
- Mackenzie J "Pulsations in the Veins with the Description of a Method for Graphically Recording Them" *J Path & Bact* 1893 I 53
- The Study of the Pulse Arterial Venous and Hepatic and of the Movements of the Heart* Macmillan Co New York and London 1902
- "The Ink Polygraph" *Brit M J* 1908 I 1411

- Mann H "Study of Peripheral Circulation by Means of an Alternating Current Bridge" *Proc Soc Exper Biol & Med* 1937 XXXVI 670
- Marey E J "Recherches sur l'état de la circulation d'après les caractères du pouls fournis par un nouveau sphygmographe" *J de la physiol de l'homme* Paris 1860 III 241
- Miller A and White P "Crystal Microphone for Pulse Wave Recording" *Am Heart J* 1941 XXI 504
- Morgagni J "De Sedibus et Causis Morborum Ex typog Remondiniani Venice 1761
- Nyboer J "Electrical Impedance Plethysmography A Physical and Physiologic Approach to Peripheral Vascular Study" *Circulation* 1950 II 811
- Potain P C E "Des mouvements et des bruits qui se passent dans les veines jugulaires" *Bull et mem Soc méd d'hop d Paris* 1867 IV 2eme serie pp 3-27 of the *Memoires of the Society*
- Puddu V "Rheumatic Heart Disease with Normal Rhythm and Very Large a Waves in the Jugular Pulse" *Am Heart J* 1951 XLI 708
- Taquini A C "The Esophageal Pulse under Normal and Abnormal Conditions" *Am Heart J* 1940 XV 129
- Vierordt K "Die Lehre von Arterienpuls in gesunden und kranken Zuständen" Friedrich Vieweg und Sohn Braunschweig 1855
- Vissel W "Die Inversion des Rheokardiogramms zugleich ein Beitrag zur Kenntnis der extracardialen Beeinflussbarkeit der Kurve" *Wien Ztschr für inn Med und ihre Grenzgebiete* 1948 XXIX 341
- Wenckebach K F "Die Arrhythmie als Ausdruck bestimmter Funktionsstörungen des Herzens" W Engelmann Leipzig 1903
- White P D and Cooke W T "The Recognition and Significance of Marked and Chronic Systolic Pulsation of the Deep Jugular Veins" *Tr A Am Physicians* 1939 LIV 199

### Ballistocardiography

- Abramson E "Die Rückstosskurve des Herzens (Kardiodynamogramm): Skandinav" *Arch f Physiol* 1933 LXVI 191
- Brown H R Jr Hoffman M J and deLalla V Jr "Ballistocardiograms in Coarctation of the Aorta" *New England J Med* 1949 CCXL 715
- Cournand A Ranges H A and Riley R L "Comparison of the Results of the Normal Ballistocardiogram and a Direct Fick Method in Measuring the Cardiac Output in Man" *J Clin Investigation* 1942 XXI 287
- Dock W and Taubman P "Some Techniques for Recording the Ballistocardiogram Directly from the Body" *Am J Med* 1949 VII 751
- Dow P and Hamilton W F "An Analysis by Hydraulic Models of the Factors Operating to Produce the Typical Ballistocardiogram" *Am J Physiol* 1941 CXXXIII 263
- Gordon J W "Certain Molar Movements of the Human Body Produced by the Circulation of the Blood" *J Anat & Physiol* 1877 XI 533
- Hamilton W F and Dow P "Cardiac and Aortic Contributions to the Human Ballistocardiogram" *Am J Physiol* 1941 CXXXIII 313
- Hamilton W F Dow P and Remington J W "The Relationship Between the Cardiac Ejection Curve and the Ballistocardiographic Forces" *Am J Physiol* 1945 CXLIV 557
- Henderson Y "The Mass Movements of the Circulation as Shown by a Recoil Curve" *Am J Physiol* 1905 XIV 287
- Kralik V E "The Electric Strain Gauge Ballistocardiograph" *Am Heart J* 1950 XXXIX 161
- Mathers J A L Nickerson J L Fleming T C and Patterson M C "Abnormal Ballistocardiographic Patterns in Cardiovascular Disease as Recorded with the Low Frequency Critically Damped Ballistocardiograph" *Am Heart J* 1950 XL 390
- Nickerson J L "The Ballistocardiographic Pattern with Special Reference to the H Wave" *Am Heart J* 1949 XXXVII 656
- Nickerson J L and Curtis H J "Design of Ballistocardiograph" *Am J Physiol* 1944 CXLII 1
- Starr I and Maycock R L "On the Significance of Abnormal Forms of the Ballisto-

cardiogram A Study of 234 Cases with 40 Necropsies" *Am J M Sc* 1948 CCXV 631

Starr I Rawson A J Schroeder H A and Joseph N R "Studies on the Estimation of Cardiac Output in Man and of Abnormalities in Cardiac Function, from the Heart's Recoil and the Blood's Impacts the Ballistocardiogram" *Am J Physiol* 1939 CXXVII 1

Starr L and Schroeder H A Ballistocardiogram II Normal Standards Abnormalities Commonly Found in Diseases of the Heart and Circulation and Their Significance *J Clin Investigation* 1940 XIX 437

Wilkins R W A Tilting Ballistocardiograph *Am Heart J* 1943 XXVI 351

### Capillary Circulation and Pulsation

Crawford J H and Rosenberger H "Studies on Human Capillaries I An Apparatus for Cinematographic Observation of Human Capillaries" *J Clin Investigation* 1936, II 343

II Observations on the Capillary Circulation in Normal Subjects *Ibid* p 351

III Observations in Cases of Auricular Fibrillation *Ibid* p 365

Danzer C S and Hooker D R "Determination of the Capillary Blood Pressure in Man with the Microcapillary Tonometer" *Am J Physiol* 1920 LII 136

Eichna L W Capillary Blood Pressure in Man Direct Measurements in the Digits During Arterial Hypertension Induced by Paredrinol Sulfate" *J Clin Investigation* 1942 XXI 731

Capillary Blood Pressure in Man Direct Measurements in the Digits of Patients with Raynaud's Disease and Scleroderma Before and After Sympathectomy *Am Heart J* 1943 XXV 812

Eichna L W and Bordley J III Capillary Blood Pressure in Man Comparison of Direct and Indirect Methods of Measurement *J Clin Investigation* 1939 XVIII 695

Capillary Blood Pressure in Man Direct Measurements in the Digits of Normal and Hypertensive Subjects during Vasoconstriction and Vasodilatation Various Induced *Ibid* 1942 XXI 711

Grant R T Observations on Direct Communications Between Arteries and Veins in the Rabbits Ear *Heart* 1930-31 XV 281

Grant R T and Bland F F Observations on Arteriovenous Anastomoses in Human Skin and in the Bird's Foot with Special Reference to the Reaction to Cold" *Heart* 1931 XV 385

Krogh A *The Anatomy and Physiology of Capillaries* Yale University Press New Haven 2nd ed 1929 (1st ed 1922)

Landis E M Micro Injection Studies of Capillary Blood Pressure in Human Skin *Heart* 1930 XV 209

Capillary Pressure and Capillary Permeability *Physiol Rev* 1934 XIV 404

"The Capillaries of the Skin Review" *J Invest Dermat* 1938 I 295

Lewis T *The Blood Vessels of the Human Skin and Their Responses* Shaw & Sons Ltd London 1927

Lombard W F The Blood Pressure in the Arterioles Capillaries and Small Veins of the Human Skin *Am J Physiol* 1911-12 XXIX 335

Malpighi M *De pulmonibus observationes anatomicae* Bologna 1661

Pappenheimer J E and Soto-Rivera A "Effective Osmotic Pressure of the Plasma Proteins and Other Quantities Associated with the Capillary Circulation in the Hindlimbs of Cats and Dogs" *Am J Physiol* 1948 CLII 471

Richards A N and Schmidt C F "A Description of the Glomerular Circulation in the Frog's Kidney and Observations Concerning the Action of Adrenalin and Various Other Substances Upon It" *Am J Physiol* 1924 LXVI 178

---

## CHAPTER 9

---

# ELECTROCARDIOGRAPHY

---

One of the interesting medical achievements of our time has been the rapid indeed one might say dramatic growth of electrocardiography (ηλεκτροις amber friction of which gives rise to an electrical charge καρδια heart and γραφειν to write) To those of us who received our initial training in this field in the early days of clinical electrocardiography this evolution has been both gratifying and impressive not to say at times confusing The confusion has been due to two factors first the absence at the beginning of an adequate application of fundamental physical laws and principles so that the early growth was more empirical than scientific and second the lack of uniform technic and nomenclature utilized by various workers in the field This vigorous independence of thought and action has however its good side and agreement about utilization of the most satisfactory viewpoints and criteria will naturally follow We are still in the very midst of considerable new research and development in electrocardiography It would be impossible for me in the limited space available in this new edition to expand the chapter sufficiently to present the subject in all of its current detail I shall retain the story of the evolution of clinical electrocardiography with a brief survey of its present status and refer the reader for a more complete description of technic debatable theories and current research to the numerous monographs now available and listed in the Bibliography at the end of the chapter

Electrocardiography is one of the most important methods of cardiovascular examination ranking in value third after history taking and physical examination Like cardiovascular roentgenology it has continued to develop rapidly as the result of concentrated study in the past decades

Near the end of the eighteenth century Galvani and Volta and their followers began their important studies on electricity by utilizing that produced by animals Galvani for example in 1791 used the electrical organ of the torpedo-fish to stimulate not only the muscles and nerves of the frog but also the heart itself

About the middle of the last century it was learned in the ex

laboratory that when the pigeon's or the frog's heart contracted it produced an electric current (Matteucci 1843 Kolliker and Muller 1856) For many years after this discovery the heart current of laboratory animals was studied with the crude apparatus at that time available

Matteucci Ch Sur le courant électrique des muscles des animaux vivants récemment tues *Comptes Rendus des Seances de l'Academie des Sciences* 1843 XVI 197

1 The signs of the electrical current of the frog itself demonstrated by the galvanometer increase in the same instrument in the act of contraction

2 The muscular electrical current which I shall hereafter call the muscular current is present in all muscle masses whatever the animal

I have taken pectoral muscles of pigeons a rabbit's back muscles hearts of pigeons In all cases I have obtained a current which flows from the interior of the muscle to the surface (Translation by myself)

Kolliker A and Muller H Nachweis der negativen Schwankung des Muskelstroms am natürlich sich contrahirenden Muskel *Verhandlungen der physikalisch medicinischen Gesellschaft in Würzburg* 1856 VI 528

The results which up to now we have obtained from the frog's heart are as follows

1 The apex of the whole heart is electrically negative to any point on the anterior or posterior surface of the ventricles

2 Similarly negative is the apex of the heart to the cut surfaces left after removing the auricles without injury to the ventricles

3 On the other hand the cardiac apex is positive to any cross section which involves the ventricular musculature itself

4 Every point on the surface of the heart is positive to any selected cross section of the ventricle

5 The excursion given by connecting the outer surfaces of the base and of the apex of the heart is less than that given by connecting the cross section of the apex and the surface (Translation by myself)

Then came the discovery six decades ago also in the physiologic laboratory that the human heart current could be demonstrated by connecting the outside of the body by electrodes with the capillary electrometer (Waller 1887)

Waller A A Demonstration on Man of Electromotive Changes Accompanying the Heart's Beat *J Physiol* 1887 VIII 229

If a pair of electrodes (zinc covered by chamois leather and moistened with brine) are strapped to the front and back of the chest and connected with a Lippmann's capillary electrometer the mercury in the latter will be seen to move slightly but sharply at each beat of the heart If the movements of the column of mercury are photographed on a travelling plate simultaneously with those of an ordinary cardiographic lever a record is obtained as under (fig 1) in which the upper line h h indicates the heart's movements and the lower line l l the level of the mercury in the capillary Each beat of the heart is seen to be accompanied by an electrical variation [This very first published electrocardiogram is essentially

the chest lead reintroduced as Lead 4 into clinical electrocardiography in recent years ]

The first and chief point to determine is whether or no the electrical variation is physiological and not due to mechanical alteration of contact between the electrodes and the chest wall caused by the heart's impulse. To ascertain this point accurate time measurements are necessary a physiological variation should precede the movement of the heart while this could not be the case if the variation were due to altered contact. Fig. 2 is an instance of such time measurements taken at as high a speed of the travelling surface as may be used without rendering the initial points of the curves too indeterminate. It shows that the electrical phenomenon begins a little before the cardiographic lever begins to rise.

That a true electrical variation of the human heart is demonstrable may further be proved beyond doubt by leading off from the body otherwise than from the chest wall. If the two hands or one hand and one foot be plunged into two dishes of salt solution connected with the two sides of the electrometer the column of mercury will be seen to move at each beat of the heart though less than when the electrodes are strapped to the chest. The hand and foot act in this case as leading off electrodes from the heart and by taking simultaneous records of these movements of the mercury and of the movements of the heart it is seen that the former correspond with the latter slightly preceding them and not succeeding them as would be the case if they depended upon pulsation in the hand or foot. This is unquestionable proof that the variation is physiological for there is here no possibility of altered contact at the chest wall and any mechanical alteration by arterial pulsation could only produce an effect 0.15" to 0.20" after the cardiac impulse. A similar result is obtained if an electrode be placed in the mouth while one of the extremities serves as the other leading off electrode. The electrical variation precedes the heart's beat as in the other cases mentioned.

The mercury column moved up and down several times with each heartbeat but the records obtained by photographing its shadow were inaccurate because of the inertia of the instrument. Laboriously the electric heart tracings or electrocardiograms were obtained and corrected and considerable progress in their analysis was made by physiologists at the end of the last century (Bayliss and Starling 1892) and at the beginning of the present century. Finally in 1903 came the announcement of the invention of the accurate and practicable string galvanometer (Einthoven) a few years later this was introduced into hospitals and clinical electrocardiography began.

Einthoven W. Die galvanometrische Registrirung des menschlichen Elektrokardiogramms zugleich eine Beurtheilung der Anwendung des Capillar Elektrometers in der Physiologie. *Pflüger's Arch f d ges Physiol* 1903 XCIX 472

(Page 474) I have tried to find a way to avoid as far as possible the construction of a new curve [that is a corrected curve such as it was necessary to construct in the use of the capillary electrometer] in so doing I have at length devised an instrument which satisfies many requirements and is especially suitable to inscribe the human electrocardiogram directly in almost its exact proportions.

The essential part of this instrument—the string galvanometer—is a thin silver coated quartz fibre which is stretched like a string in a strong magnetic field. If

an electric current is led through this quartz fibre the fibre shows a movement which can be observed and photographed by means of considerable magnification, just as is the case with the movement of the mercury in the capillary electrometer. It is possible to regulate the sensitivity of the galvanometer very accurately within wide bounds by tightening and loosening the string (Translation by myself)

During the past three decades with the development of audion tube amplification the dead beat mirror galvanometer has been adapted to clinical electrocardiography and is the basis for much of the easily portable apparatus that can be carried to the sickroom for cardiac registration of patients at home in bed. The cathode ray has also been utilized to record the electrical activity and sounds of the heart in man but it is unnecessarily expensive in cost and in the use of high operating voltage for the needs of clinical electrocardiography and phonocardiography although in current research it is being utilized with extensive chest leads to explore details of the course of electrical discharge and repolarization through the heart muscle (Goldman) \*

A recent innovation has been the utilization of an ingenious device of a heated stylus which activated by a galvanometer moves without friction or overshooting over the surface of a moving processed (wax covered) paper strip to inscribe the electrocardiogram directly without the trouble time and expense of photographic technic. This type of direct writing electrocardiograph has the advantage of accuracy in recording over the initial ink writing galvanometers which were originally introduced to simplify the clinical technic.

At first electrocardiography was sought and used chiefly as an aid in the explanation of cardiac arrhythmia tachycardia and bradycardia having proved to be more satisfactory than the mechanical graphic methods previously employed because of the greater ease of technic and interpretation and because of the more complete information afforded. As time went on however it was learned that more important data about the heart than the explanation of abnormalities of rate and rhythm are shown by the electrocardiogram from a study of the shape direction amplitude and time relations of the individual waves or deflections especially as they are compared in various leads.

It is unfortunate that we do not even as yet know the range of the normal electrocardiogram it is wider than we thought it was ten years ago and much service can still be wrought by the simple electrocardiographic analysis of many thousands of normal individuals. It is also important to become familiar with the electrocardiogram in infancy which is different from that in older children and adults not only in much faster heart rate but in much narrower time intervals especially *P R* interval and *QRS* duration (shorter by one third to one half—see Figure 54 page 214) and in its normal right axis deviation. It is interesting that the human infant's type of electrocardiogram becomes recognizable at the end of the first month of fetal life (Marcel and

Recently cathode ray electrocardiography by radio (remote control) has been introduced by Holter of Helena Montana (1949) and by Kanatsoulis of Athens Greece (1950)

Exchaquet 1938) also exploration of the maternal abdomen to obtain fetal electrocardiograms has been found successful in 85 to 90 per cent of cases (Goodyear et al 1942)

*The electrocardiograph does not take the place of such other methods of examination as history taking percussion auscultation and roentgenology but it does obviate in large part the need of taking mechanical graphic records of arterial and venous pulses and of the apex impulse Finally it must be realized that the electrocardiogram may be perfectly normal even in the presence of serious heart disease This method of study should therefore be viewed modestly as helpful but not accorded too great importance*

The electrocardiogram itself is written by the spread of electrical activity that sweeps down the heart from its pacemaker at each heartbeat in peristaltic waves over the atria and by special conduction tracts and fibers into the ventricles (Figure 39)

It is the movement of the string shadow or beam of light that causes the waves (usually called deflections or complexes) of the electrocardiogram

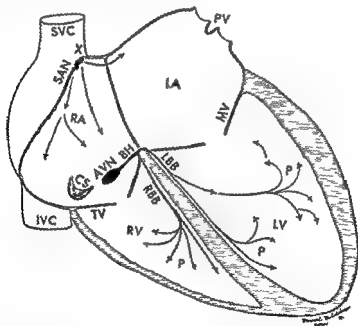


FIG 39 Diagram of excitatory and conduction system of the heart

SVC superior vena cava  
IVC inferior vena cava  
RA right atrium  
CS coronary sinus  
TV tricuspid valve  
RV right ventricle  
PV pulmonary veins  
LA left atrium  
MV mitral valve

LV left ventricle  
SAN sinoatrial node  
X usual site of pacemaker  
AVN atrioventricular node  
BH bundle of His  
RBB right bundle branch  
LBB left bundle branch  
P Purkinje network radiating out from papillary muscles



These waves chiefly three have been variously named. The German school at first labeled them  $\alpha$  for atrial wave,  $i$  for the first or initial ventricular wave and  $f$  for the second or final ventricular wave. These designations have been justified by time but they have not been generally adopted. Einthoven's letters arbitrarily taken from the middle of the alphabet and attached to the deflections so as not to prejudice future workers in the study of the cardiac mechanism have become universally employed and will be used here. The first deflection or atrial wave is called  $P$ , the second deflection or the first ventricular wave a rapid succession of one, two or three deflections is called  $Q$ ,  $R$  and  $S$  and the third deflection or second ventricular wave is called  $T$  (Figure 40). There is often a small final and unexplained wave called  $U$ .

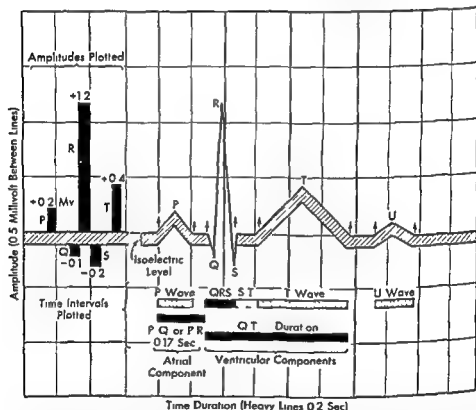


FIG 40 Diagram of normal electrocardiogram showing the individual complexes with special reference to amplitude and time duration  $P$  = atrial deflection  $QRS$  = first ventricular deflection  $ST$  segment and  $T$  wave = remainder of ventricular activity beginning of  $Q$  to end of  $T$  = duration of systole

There are two essential methods of description of the normal and abnormal electrocardiogram (1) that of the detailed analysis of the individual complexes or waves which will be largely covered in the present chapter and (2) that of the presentation of the characteristics of the records as a whole that is of the patterns which will be presented largely in other chapters for

example the electrocardiographic patterns of certain congenital defects of mitral stenosis of the hypertensive heart and the cor pulmonale of pericarditis and of myocardial infarction

### ELECTROCARDIOGRAPHIC LEADS

The first and fundamental step in studying electrocardiograms is to become familiar with the so called electrocardiographic leads. An electrocardiographic lead is the connection of any two parts of the body by electrodes and wires with the recording galvanometer. Although two electrodes may be attached to any parts of the body (if they are not both too far from the heart or too close together) to lead the heart current to the galvanometer it has become customary for convenience and other reasons to make use clinically of the forearms the left leg and the precordium. An esophageal lead point to explore the left atrium and base and posterior portion of the left ventricle has been proposed and tried with results of some interest but the procedure is not clinically practicable.

Direct leads from various points on the heart surface itself present the most detailed information possible concerning the spread of the excitation wave and aberrations thereof to the individual heart chambers and their anterior posterior and lateral walls. The best substitute for such direct leads in man has been found to be precordial leads with exploring electrode placed on the skin as directly as possible over the part of the heart which it is desired to study. Thus many thoracic lead points are possible in the various intercostal spaces and around the chest and even in the esophagus. We have not yet nearly enough information to be sure of the most desirable positions and indeed they are already known to vary from person to person according to the body build and the position and type of heart disease but certain points have already been selected and made the object of considerable study in normal and abnormal subjects more about these below. An important consideration in obtaining these precordial or close up leads is that the other or as it is sometimes called indifferent remote or peripheral electrode should be placed far from the heart itself on one of the extremities or on the back or by an ingenious arrangement introduced by Wilson to neutralize the effect of any one extremity by connecting all four extremities to a central terminal as the remote electrode point. The concentration of interest on the precordial leads initiated what has been called essentially a unipolar lead.

Quickly following suit unipolar limb leads have been introduced to join the unipolar and bipolar chest leads they were at first in major part elaborated by Goldberger (1947). In the early days of these so-called unipolar limb leads it was thought that they had a rather mysterious superiority over the old classical bipolar limb leads particularly in revealing more accurately the electrical (and also often the anatomic) position of the heart and otherwise obscure myocardial disease but more recently it has been shown by Gr and others that they actually merely supplement the bipolar limb

allow us to establish with greater accuracy the projection of the axis and abnormalities thereof on the frontal plane of the thorax thus expanding Einthoven's triangle (see below) into a figure with six axes the three of the unipolar leads being perpendicular to the three of the bipolar leads so that there is only a 60 degree instead of a 120 degree interval between the axes (as will be illustrated later in the chapter)

Although the very first published electrocardiogram (Waller 1887) was a chest lead convenience and chance led early electrocardiographers away from the thorax itself to limb connections and only in late years has there been a return to the precordium as an important focus of attention. The precordial leads at this writing (1950) appear to have a double value as compared with the limb leads they reveal the electrical axis projection on the anteroposterior (more or less sagittal) plane at right angles to the frontal plane thus completing the resultant projection of the direction and magnitude of the electrical axis in space but also because of their close proximity to the heart itself they show more clearly myocardial abnormalities closest to the heart. Nevertheless it is not likely that the limb leads as now taken will be abandoned soon inasmuch as they readily reveal normal variations and abnormalities in the frontal plane. The heart is a solid body and so should be explored electrically from all directions. Eventually techniques such as those developed by Duchosal and by Goldman (see below) or something newer still may replace the present procedures but as yet they have not been developed for practical routine use.

In summary the reasons for taking these three types of leads are as follows. We continue to register the *bipolar limb leads* because we are familiar with them after many years of use, because they clearly suffice to demonstrate the mechanisms responsible for tachycardia bradycardia and arrhythmia because they are important in helping to establish the projection of the electrical axis and abnormalities thereof in the frontal plane and because they have become in many instances a part of the useful electrocardiographic patterns with which we have become familiar during the past decade such as those of the acute cor pulmonale congenital atrial septal defect and advanced mitral stenosis (or chronic constrictive pericarditis involving preponderantly the left heart chambers). The *unipolar limb leads* are registered because they are especially helpful in demonstrating the position of the heart with or without complications of heart disease itself thus the right arm lead always (except in cases with dextrocardia) faces the interior of the heart and so normally all its complexes are inverted the left arm faces the outside wall of the heart when the heart lies horizontally or diagonally with resultant upright complexes and the inside of the heart (as does the right arm lead) when the heart is vertical giving inverted QRS and T waves the left leg lead never faces the inside of the heart although it is at right angles to its axis when it lies horizontally thus yielding under such conditions small almost isoelectric complexes. The *unipolar precordial leads* are registered because of their double value just discussed in the preceding paragraph.

Thus ordinarily now the three bipolar and the three unipolar limb leads

and several (preferably six) precordial leads are registered for each patient studied these leads have been called Leads 1 2 3 aVR aVL aVF and Precordial or Chest Leads 1 to 6 or more respectively (Figure 41) In routine interpretation at the present time (1951) it is convenient to analyze first the precordial leads since they often give the most information

### BIPOLAR ( CLASSICAL ) LIMB LEADS

*Lead I* consists of the connection of the right lower arm to one end of the galvanometer string and of the left lower arm to the other end so that the preponderant spread of the action current (which has been called the wave

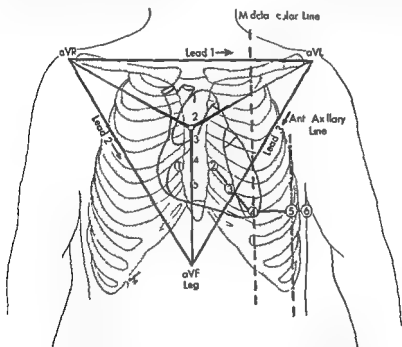


FIG 41 Diagram showing bipolar limb leads (1 2 3) unipolar limb leads (aVR aVL aVF) and precordial leads (V to V inclusive) The outline of the heart is shown under the sternum and ribs the level of the first five interspaces is indicated Einthoven's triangle is represented as is also the spatial relationship of the remote electrode to the limb electrodes in the case of the unipolar limb leads

of relative negativity) in the direction of the lead that is from right arm to left is represented normally in the electrocardiogram by an upright deflection of the string shadow while its reverse direction is represented by an inverted deflection

*Lead 2* consists of a similar arrangement but with electrodes on right arm and left leg Either leg may be used with little or no change in the records obtained since both legs show almost the same difference of electric potential

allow us to establish with greater accuracy the projection of the axis and abnormalities thereof on the frontal plane of the thorax thus expanding Einthoven's triangle (see below) into a figure with six axes the three of the unipolar leads being perpendicular to the three of the bipolar leads so that there is only a 60 degree instead of a 120 degree interval between the axes (as will be illustrated later in the chapter)

Although the very first published electrocardiogram (Waller 1887) was a chest lead convenience and chance led early electrocardiographers away from the thorax itself to limb connections and only in late years has there been a return to the precordium as an important focus of attention. The precordial leads at this writing (1950) appear to have a double value as compared with the limb leads they reveal the electrical axis projection on the anteroposterior (more or less sagittal) plane at right angles to the frontal plane thus completing the resultant projection of the direction and magnitude of the electrical axis in space but also because of their close proximity to the heart itself they show more clearly myocardial abnormalities closest to the heart. Nevertheless it is not likely that the limb leads as now taken will be abandoned soon inasmuch as they readily reveal normal variations and abnormalities in the frontal plane. The heart is a solid body and so should be explored electrically from all directions. Eventually techniques such as those developed by Duchosal and by Goldman (see below) or something newer still may replace the present procedures but as yet they have not been developed for practical routine use.

In summary the reasons for taking these three types of leads are as follows. We continue to register the *bipolar limb leads* because we are familiar with them after many years of use because they clearly suffice to demonstrate the mechanisms responsible for tachycardia bradycardia and arrhythmia because they are important in helping to establish the projection of the electrical axis and abnormalities thereof in the frontal plane and because they have become in many instances a part of the useful electrocardiographic patterns with which we have become familiar during the past decade such as those of the acute cor pulmonale congenital atrial septal defect and advanced mitral stenosis (or chronic constrictive pericarditis involving preponderantly the left heart chambers). The *unipolar limb leads* are registered because they are especially helpful in demonstrating the position of the heart with or without complications of heart disease itself thus the right arm lead always (except in cases with dextrocardia) faces the interior of the heart and so normally all its complexes are inverted the left arm faces the outside wall of the heart when the heart lies horizontally or diagonally with resultant upright complexes and the inside of the heart (as does the right arm lead) when the heart is vertical giving inverted *QRS* and *T* waves the left leg lead never faces the inside of the heart although it is at right angles to its axis when it lies horizontally thus yielding under such conditions small almost isoelectric complexes. The *unipolar precordial leads* are registered because of their double value just discussed in the preceding paragraph.

Thus ordinarily now the three bipolar and the three unipolar limb leads

possible over the cardiac apex. However, it rather quickly became apparent that even with care it was not always possible so to place II that even though it were so placed it would usually emphasize normality or abnormalities of but a localized area of the heart wall and that it might be so close to the ventricular sulcus or so perpendicular to the spatial axis of the heart that a slight displacement to either side would shift its position from one ventricle to the other or from negative to positive side of the anteroposterior plane of the thorax (or vice versa) with a great change in the pattern. Therefore an isolated Lead 4 was given up by most workers in the field a few years ago.

It was also stated in the last edition of this book that multiple precordial (chest) leads should be taken in special or doubtful cases and that the author and his colleagues were taking three such leads (CF, CF<sub>4</sub> and CF<sub>6</sub>) when necessary, rarely more at that time. Our own experience and that of many others soon caused us to take three precordial leads routinely with the exploring electrode at points 2, 4 and 5 and as time went on over 2, 4 and 5 instead and with Wilson's central terminal (V) for the indifferent lead point instead of the left leg (as had been our choice) or the right arm (as was often the choice of others). Finally, with more experience in the course of time we began to take all six precordial V leads in addition to the six limb leads mentioned above so that for the sake of the valuable extra information afforded we now take 12 routine leads instead of the 3 that we took at the time of the first edition of this book (1931), the 4 that we frequently took at the time of the second edition of the book (1937) and the 6 that was our custom at the time of the third edition of the book (1944). In fact on occasion we may now explore further still, as in the case of a special atrial lead (high up over the right atrium) or of a lead (sometimes called 7) on the back at the left posterior axillary line. It is still too early to know how far we had best explore and just what techniques we shall eventually use.

Multiple precordial leads (Figure 41) have become standardized as follows: the prefix depending on the position of the indifferent electrode or lead point—CR (chest—right arm), CL (chest—left arm), CF (chest—left leg) and CV usually abbreviated now to V.

1 or CR<sub>1</sub>, CL<sub>1</sub>, CF<sub>1</sub>, CV<sub>1</sub> or V<sub>1</sub>—the exploring electrode at the *right* border of the sternum in the fourth intercostal space.

2 or CR<sub>2</sub>, CL<sub>2</sub>, CF<sub>2</sub>, CV<sub>2</sub> or V<sub>2</sub>—the exploring electrode at the *left* border of the sternum in the fourth intercostal space.

3 or CR<sub>3</sub>, CL<sub>3</sub>, CF<sub>3</sub>, CV<sub>3</sub> or V<sub>3</sub>—the exploring electrode midway on the line joining 2 and 4.

4 or CR<sub>4</sub>, CL<sub>4</sub>, CF<sub>4</sub>, CV<sub>4</sub> or V<sub>4</sub>—the exploring electrode at the left mid clavicular line in the fifth intercostal space. We used to try to place this electrode at the cardiac apex but the variability of the position of the latter both in health and in disease rendered that location very unreliable and unsatisfactory.

5 or CR<sub>5</sub>, CL<sub>5</sub>, CF<sub>5</sub>, CV<sub>5</sub> or V<sub>5</sub>—the exploring electrode at the anterior

during the cardiac cycle the left leg is however the customary lower point

Lead 3 consists of the connection of the galvanometer with left arm left leg in comparison with Lead 2 the left leg lead continues to be the contact while the left arm is substituted for the right arm

Thus these three lead points right arm left arm and left leg when connected form a triangle which is essentially equilateral Electrically and electrometrically Lead 2 is equal to the sum of Leads 1 and 3 since the difference of electric potential between right arm and left leg is the same whether you connect the lead points directly or in a roundabout way Therefore the  $P_1$  should equal  $P_2$  plus  $P_3$   $QRS$  should equal  $QRS_1$  plus  $QRS_3$  and  $T$  should equal  $T_1$  plus  $T_3$  (these letters refer to atrial and ventricular deflections in the electrocardiogram soon to be discussed while the appended numbers refer to the particular leads—1 2 and 3) Similarly Lead 2 minus Lead 1 equals Lead 3 and Lead 2 minus Lead 3 equals Lead 1 This fact although useful clinically in checking the accuracy of standardization of the various leads is often ignored

### UNIPOLAR LIMB LEADS

Lead *aVR* is the new customary so called augmented (a) that is amplified 50 per cent unipolar (V a symbol) right arm (R) lead The exploring electrode is attached to the right arm and connected to one pole of the galvanometer while the other pole is connected to the indifferent lead point which in the case of the unipolar limb leads has been found to serve best when attached to the three limbs not being explored V is a designation introduced by Johnston—personal communication 1951—to indicate leads taken with a central terminal and derived from its usage by electrical engineers and physicists as a symbol of electrical potential it was not originally intended as an abbreviation for vector

Lead *aVL* is the augmented unipolar left arm lead with exploring electrode on the left arm and indifferent lead point connected to the right arm and both legs

Lead *aVF* is the augmented unipolar left leg (F for foot) lead with exploring electrode on the left leg and indifferent lead point connected to both arms and right leg

It is important and convenient to know that when added together the three unipolar limb leads *aVR* *aVL* and *aVF* equal zero

### PRECORDIAL (CHEST OR THORACIC) LEADS

In the last (third) edition of this book much was said about Lead 4 which had been called the standard or indeed even the "classical" chest lead It had been taken by attempting to place the exploring electrode as near as

ighth and ninth leads over the left back and right anterior chest leads numbered from midline to the right like the precordial leads and as advised by Kisch with the first lead point at the midsternum (level of fourth interspace) for both sides

It is obvious that the unipolar chest leads taken as Wilson has recommended (CV) leads give a more accurate appraisal of the potential at the various precordial lead points than do the bipolar leads although there is by no means so great a difference as in the case of the unipolar and bipolar

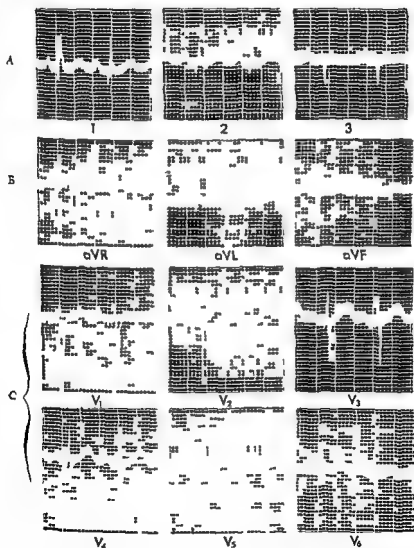


FIG 43 Electrocardiogram of normal individual of heavy build with horizontal heart position (A) Bipolar limb leads 1 2 and 3 (B) unipolar limb leads aVR, aVL, and aVF (C) six precordial leads V to V inclusive Time = 0.04 and 0.20 second amplitude 1 mm = 0.10 mv



limb leads. This is of course due to the fact that the greater the difference in distance of two electrodes from the heart the less the error due to the potential of the point to which the indifferent electrode is attached. Thus the bipolar chest leads described above approach in accuracy the unipolar chest leads of Wilson. For this reason and especially for the sake of universal uniformity it is suggested that for routine use the V leads be now employed as has been my own recent custom.

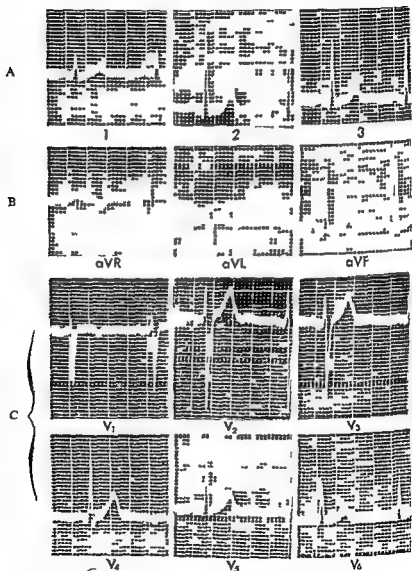


FIG. 44. Electrocardiogram of normal tall individual with vertical heart position. (A) Bipolar limb leads 1, 2, and 3. (B) unipolar limb leads  $aVR$ ,  $aVL$ , and  $aVF$ . (C) six precordial leads  $V_1$  to  $V_6$  inclusive. Time = 0.04 and 0.20 second. amplitude mm = 0.10 mv.

Intracardiac and esophageal leads have been used in research and for study of very special cases the former during catheterization of the right atrium and right ventricle and the latter for exploration of the left atrium and posterior wall of the left ventricle. They serve as unipolar leads to explore these particular parts of the heart and although during acute myocardial infarction it is not wise to subject the patient to esophageal electrocardiography it is possible in chronic cases to identify a posterior myocardial scar and also to uncover atrial action not apparent in other leads. The right intra atrial electrocardiogram shows normally an inverted *P* wave high in the atrium in the vicinity of the *S*-*A* node, an upright *P* wave low in the atrium and a diphasic *P* wave in intermediate positions while the ventricular complex varies from a *QS* to a *QR* most commonly or even less often (near the ventricle) to a *RS* all with negative *T* waves. The right intraventricular electrocardiogram shows normally an upright *P* wave and an *RS* with a negative *T*. Esophageal leads show a slightly later *P* wave over the left atrium by about 0.05 second than the *P* wave recorded by the right intra atrial electrode.

In the esophageal lead the *P* wave is as a rule unusually prominent and high and the *QRS* and *T* waves are normally inverted unless the polarity is reversed in which case an inverted *T* wave is indicative of disease (usually infarction) of the posterior wall of the left ventricle.

### CARDIAC VECTOR AND ELECTRIC AXIS

A vector is a force which has direction and magnitude and electrically either a negative or a positive charge. In electrocardiography it has been loosely called the electrical axis of the heart. Fundamentally electrocardiography is the analysis of the cardiac electrical vectors and there are various techniques for their demonstration all of which are more or less crude and in the process of further development including the old classical bipolar limb leads with the much debated but still scientifically applicable Einthoven triangle, the unipolar limb leads, the precordial leads and the more basic but least developed technique of all namely that of vectorcardiography.

When the excitation wave spreads from normal or abnormal pacemaker through the heart it is attended by a wave of electric activity which takes a complicated manifold path (see Figure 39 page 183). The diffuse course can be represented by the *QRS* loop, a curve not lying in a single plane but in space as does the heart itself. A further reduction of this curve has hitherto been necessary to suit the limited boundaries of electrocardiography and so we can determine its projection on the anterior plane of the body to fit into the triangle of the three classical leads or on any other plane for example specifically sagittal or horizontal. Finally for further convenience the curve is simplified by constructing its resultant, a straight line to show the consequent angle and magnitude. This resultant of the projection of the true axis of the distributed electric potential of the heartbeat is what we briefly designate as the electric axis of the electrocardiogram. It can be determined by calculation

from any two of the three classical limb leads by formula or by diagram using what is called Einthoven's triangle. It has been of some clinical interest and value to make this calculation in cases showing an abnormal deviation of the angle (the normal range of angle is from  $-20^\circ$  to  $+100^\circ$  but usually  $+90^\circ$  to  $+70^\circ$ ). The formula is as follows:  $\tan \alpha = \frac{2e - e_1}{e_1 \sqrt{3}}$  where  $\alpha$  equals the angle between the axis and the horizontal,  $e$  the amplitude in millimeters of the QRS wave in Lead 2 and  $e_1$  that of the QRS in Lead 1. The length of the axis or the manifest potential difference ( $E$ ) is calculated from the following formula:  $E = \frac{e}{\cos(\alpha - 60^\circ)}$ . More convenient than the formulas has been the employment of the diagram of the triangle of leads (Figure 45, Einthoven's triangle). Leads 1 and 3 are usually employed in this calculation. The amplitude of  $R_1 - S_1$  is plotted on the Lead 1 line and that of  $R_3 - S_3$  on the Lead 3 line. Perpendiculars are dropped from the points to their points of intersection. Lines are then drawn out from the center of the circle through these points of intersection to the circumference of the circle; the angles with the horizontal diameter of the circle, the zero line, are read off, the degrees being noted as positive around the semicircle clockwise to  $180^\circ$  and as negative counterclockwise. This is a crude but clinically convenient and useful method. It affords only a very general measurement and shows no detail of the axis deviation. If at the present time, however, greater detail and accuracy are attempted, the method becomes complicated and difficult. Although it is of some academic interest to know not only the resultant axis deviation but its whole curve—that is, the individual deviations at various phases—it is of much greater interest to know the direction of the curve in space, for example, how much of it is bent backward in the anteroposterior plane, a feature not shown at all in the frontal plane. It is to be noted that to secure adequate information accurately for even one (e.g., the frontal) plane, two electrocardiographic leads must be registered simultaneously to make sure of the synchronicity of phases; for example, the top of the QRS peak in Lead 1 is often not synchronous with either peak (or nadir) or downstroke in Lead 3. A further development of the representation and analysis of the cardiac vector (electric axis) in space has been the construction of the vectorcardiogram, both by projection on the three planes and by tridimensional models (see below).

The direction of the resultant electric axis of the heart in the frontal plane lies within wider limits than does the anatomic axis, both normally and abnormally. The normal electric axis lies between the degrees  $-20^\circ$  and  $+100^\circ$  of Einthoven's triangle (Figure 45). If the angle is more minus than  $-20^\circ$ , that is, much above the horizontal, there is so-called abnormal left axis deviation; and if it is beyond  $+100^\circ$ , that is, considerably to the right of the vertical, there is abnormal right axis deviation.

The term abnormal left and right axis deviation, as applied to the classical bipolar limb leads, does not have the same significance as left and right

ventricular preponderance. Displacement of the heart upward by a high diaphragm so that the heart lies horizontally will give abnormal left axis deviation even though the left ventricle remains normal while a low diaphragm with vertical heart position will tend to give abnormal right axis deviation even though the right ventricle is small and the left ventricle actually preponderant. It is true however that when we find high degrees of abnormal

Lead

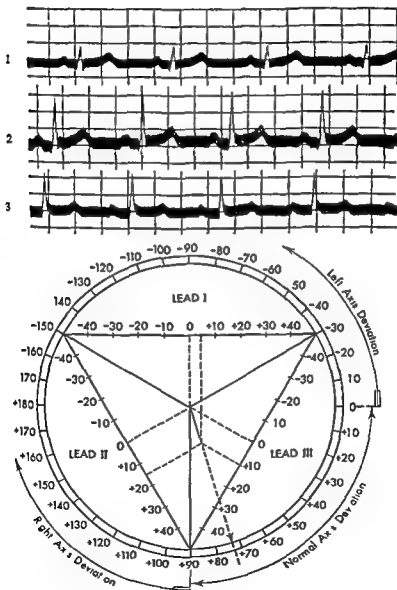


FIG. 45 Electrocardiogram (Leads I, II, and III) and Einthoven's triangle showing normal angle of the electrical axis

from any two of the three classical limb leads by formula or by diagram usually what is called Einthoven's triangle. It has been of some clinical interest and value to make this calculation in cases showing an abnormal deviation of the angle (the normal range of angle is from  $-20^\circ$  to  $+100^\circ$  but usually  $+70^\circ$  to  $+70^\circ$ ). The formula is as follows  $\tan \alpha = \frac{2e - e_1}{e_1 \sqrt{3}}$  where  $\alpha$  equals the angle between the axis and the horizontal  $e$  the amplitude in millimeters of the QRS wave in Lead 2 and  $e_1$  that of the QRS in Lead 1. The length of the axis or the manifest potential difference ( $E$ ) is calculated from the following formula  $E = \frac{e}{\cos(\alpha - 60^\circ)}$ . More convenient than these formulas has been the employment of the diagram of the triangle of the leads (Figure 45 Einthoven's triangle). Leads 1 and 3 are usually employed in this calculation. The amplitude of  $R_1 - S_1$  is plotted on the Lead 1 line and that of  $R_3 - S_3$  on the Lead 3 line. Perpendiculars are dropped from the points to their points of intersection. Lines are then drawn out from the center of the circle through these points of intersection to the circumference of the circle. The angles with the horizontal diameter of the circle the zero line are read off the degrees being noted as positive around the semicircle clockwise to  $180^\circ$  and as negative counterclockwise. This is a crude but clinically convenient and useful method. It affords only a very general measurement and shows no detail of the axis deviation. If at the present time however greater detail and accuracy are attempted the method becomes complicated and difficult. Although it is of some academic interest to know not only the resultant axis deviation but its whole curve that is the individual deviations at various phases it is of much greater interest to know the direction of the curve in space for example how much of it is bent backward in the anteroposterior plane a feature not shown at all in the frontal plane. It is to be noted that to secure adequate information accurately for even one (e.g. the frontal) plane two electrocardiographic leads must be registered simultaneously to make sure of the synchronicity of phases for example the top of the QRS peak in Lead 1 is often not synchronous with either peak (or nadir) of downstroke in Lead 3. A further development of the representation and analysis of the cardiac vector (electric axis) in space has been the construction of the vectorcardiogram both by projection on the three planes and by tridimensional models (see below).

The direction of the resultant electric axis of the heart in the frontal plane lies within wider limits than does the anatomic axis both normally and abnormally. The normal electric axis lies between the degrees  $-20^\circ$  and  $+100^\circ$  of Einthoven's triangle (Figure 45). If the angle is more minus than  $-20^\circ$  that is much above the horizontal there is so-called abnormal left axis deviation and if it is beyond  $+100^\circ$  that is considerably to the right of the vertical there is abnormal right axis deviation.

The term abnormal left and right axis deviation as applied to the classical bipolar limb leads does not have the same significance as left and right

Lead

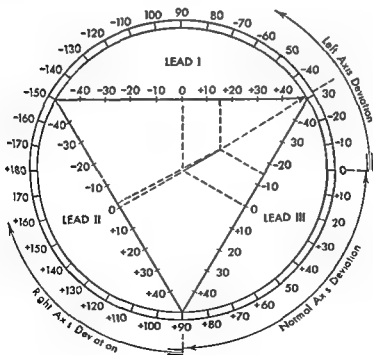
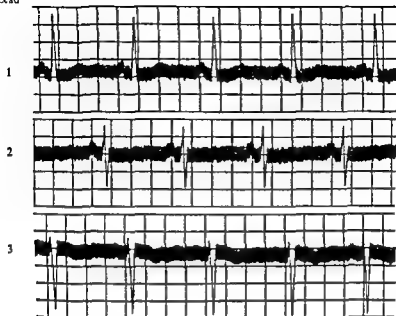


FIG 46. Electrocardiogram and Einthoven's triangle showing left axis deviation

average normal angle to an abnormal one (Figure 4 page 33) This influence of displacement may even give abnormal left axis deviation of great degree although it often but exaggerates the effect of other factors An interesting variation of this type consists of complete negativity of Lead 3 all the complexes—*P* *QRS* and *T*—being inverted this phenomenon is often found in short fat individuals with high diaphragms

2 Preponderant enlargement of the left ventricle is a common cause or accompaniment of left axis deviation of high degree Chronic hypertension and chronic aortic regurgitation or stenosis are the most important of the known clinical conditions behind it (see Figure 97 page 477 and Chapter 26)

3 Left bundle branch block (see Chapter 34) The electrocardiogram of marked left bundle branch block has abnormally wide *QRS* waves over 0.1 second in duration with moderate amplitude above the baseline in Lead 1 and below the baseline in Lead 3, with rather low voltage or diphasic *QRS* waves in Lead 2 (see Figure 165 page 947) and broad notched downwardly directed *QRS* waves over the right ventricle and bifid or slurred *R* waves over the left in the multiple precordial leads Until fifteen years ago this type of electrocardiogram was thought to indicate right bundle branch block but convincing evidence from the precordial leads (with late arrival of the intrinsic deflection over the left ventricle) exposed the error of the earlier interpretation

4 Right ventricular premature beats (see Chapter 32) Isolated instances of abnormal axis deviation occur in the form of ventricular premature beats arising in the right ventricle or near the cardiac base The *QRS* waves are deformed much as in left bundle branch block but their amplitude is usually much greater In a well marked instance of right ventricular premature beat the *QRS*<sub>1</sub> is relatively high the *QRS*<sub>2</sub> is deep the *QRS* is diphasic and often of low voltage and the precordial *QRS* shows an early intrinsic deflection over the right ventricle Years ago these extrasystoles were thought to arise in the left ventricle

*Abnormal right axis deviation* (Figure 47) much less common than abnormal left axis deviation results from five factors

1 A vertical heart position or rotation of the heart on its other axes may give rise to abnormal right axis deviation usually not of great degree the angle rarely measuring more than  $+95^\circ$  in the normal person but sufficient to mask other conditions It is by far the commonest cause of right axis deviation Deep inspiration may give temporarily a slightly abnormal right axis deviation when the electrocardiogram in quiet breathing shows a tendency toward it Displacement of the heart to one side or the other by fluid or by air in the pleura or by lung retraction or pleural adhesions affects the position of the heart as a rule in toto along with the mediastinum without causing any important change in axis deviation as does also shifting of position from one lateral recumbency to the other as noted above

2 Preponderant enlargement of the right ventricle with its attendant shift in position of the heart particularly by clockwise rotation is the commonest

Lead

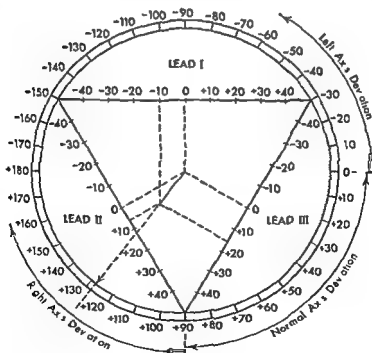
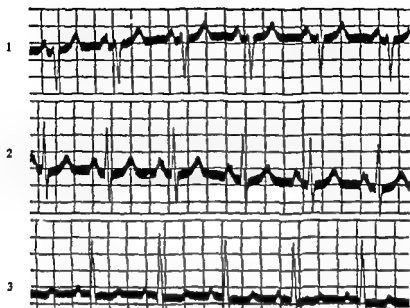


FIG 47 / Electrocardiogram and Einthoven's triangle showing abnormal right axis deviation in a case of mitral stenosis of high degree



cause of markedly abnormal right axis deviation in which there is a sharp moderately deep  $S_1$  with little or no  $R_1$ , a diphasic  $QRS$  of little voltage a high  $R_3$  with little or no  $S_3$  and relatively high  $R$  waves over the right ventricle and prominent  $S$  waves over the left ventricle in the precordial leads. During the first few weeks of life right axis deviation is often present normally in slight degree. After that age moderate or high degrees of right axis deviation are caused by three clinical conditions: mitral stenosis, congenital defects and pulmonary disease. Mitral stenosis is frequently found without abnormal right axis deviation but when that electrocardiographic sign is present especially if there is atrial fibrillation and no obvious sign of congenital heart disease that valve lesion is usually found to be present (Figure 129 page 680). Congenital pulmonic stenosis and interatrial septal defects are rarely if ever found without abnormal right axis deviation by electrocardiogram; they cause a higher degree of it than does any other condition (see Figure 73 page 320). Rarely the cause of abnormal right axis deviation is chronic pulmonary disease, in particular silicosis or other cause of extensive fibrosis. Very rarely pulmonary endarteritis may be a factor.

3 Right bundle branch block is shown electrocardiographically by abnormally wide  $QRS$  complexes directed downward in Lead 1 and upward in Lead 3 or by wide  $S_1$  waves (see Figure 166 page 948). In Lead 2 the  $QRS$  wave is diphasic as a rule and of low voltage and in the multiple precordial leads it is M shaped over the right side of the heart and shows a prominent  $R$  wave and wide  $S$  wave over the left. This was formerly called left bundle branch block (see Chapter 34).

4 Left ventricular premature beats are isolated instances of abnormal right axis deviation giving high wide  $QRS$  complexes in Leads 2 and 3.  $QRS$  waves often of low voltage, slightly or moderately inverted in Lead 1 and with wide  $QRS$  waves in the precordial leads with earlier intrinsic deflections over the left ventricle. A premature beat arising from the left ventricle although near the right ventricle has been shown experimentally to give rise to a  $QRS$  complex of left ventricular premature beat type. But ventricular premature beats are often neither of definitely right nor of definitely left ventricular type in the electrocardiogram; in such cases they may arise in the septum or junctional tissue.

5 Congenital dextrocardia shows a typical electrocardiogram in about half the cases that is where there is transposition with general situs inversus (see Figure 65 page 303). There is a complete inversion of all complexes of Lead 1 and an interchange of the usual Leads 2 and 3 due to the fact that with relation to the heart in such a case the right arm corresponds to the left arm of the person with the heart in normal position and the left arm to the right. When an electrocardiogram shows a completely inverted Lead 1 it is pathognomonic of congenital dextrocardia provided there is no error in technique, namely a crossing of electrode wires. The precordial leads show the usual normal characteristics when the exploring electrode is placed over the right side of the chest.

**Vectorcardiography** A further and natural evolution of the study of the cardiac vector is its determination and demonstration in space that is in three dimensions and also in time which is of prime importance too since the duration as well as the distance direction and magnitude of the cardiac vector is significant Various techniques have been introduced to study the vector projected on the frontal plane as already noted including among others that recently devised by Goldman using the cathode ray oscillograph and many lead points over the entire precordium which result in waves of darkness and light representing *P* *QRS* and *T* waves sweeping over the field

Also desirable as an eventual goal when it can be routinely introduced is the spatial (and time) recording of the cardiac vector which has been called vectorcardiography Various investigators have studied the problem Mann was one of the first who did so calling the resulting curve the monocardigram (1920 and 1938) Duchosal and Sulzer (1949) are also pioneer workers who have developed the method more fully with the actual construction of models of the *P* *QRS* and *T* waves (vectorcardiography) based on the projections of cathode ray oscillograms of the cardiac vector on two planes of a trihedron with the time marked off by beads attached to the wire loops representing the course of the vectors (Figure 48) Figure 49 shows the relationship of the trihedron of Duchosal and Sulzer to Einthoven's triangle and the unipolar chest lead points Much time will be needed to determine the range of normal vectorcardiograms and abnormal patterns

My friend and former associate Dr J W Hurst of Atlanta Georgia experienced in recent developments in certain techniques of the application of vectorcardiography in this country has kindly prepared for me the following insert (personal communication March 1951)

Grant and his co workers have presented a method for determining the spatial direction of the fundamental electrical forces of the heart by simple inspection of routine electrocardiographic leads Since this method appears promising it is mentioned here for completeness For greater details and proof of the method the reader is referred to the Bibliography

To determine the direction of the mean *QRS* *ST* and *T* forces in the frontal plane the six extremity leads are inspected to determine which lead has the largest deflection and which lead has the smallest deflection The resultant area of each deflection is used to determine its relative size The resultant area is determined by adding the positive portions of the curve to the negative portions algebraically The mean vector will be parallel to the lead axis with the largest resultant deflection or perpendicular to the lead axis with the smallest resultant deflection and its direction must satisfy the polarity of all six extremity leads With practice one will soon learn to interpolate between the extremes of vector positions just mentioned so that the range of error will be only 5 to 10 degrees The direction of the instantaneous vectors can be determined in a similar manner by breaking up the *QRS* and *T* deflections into small individual portions If one remembers that  $\text{Lead } I + 3 = II$  and that  $aVR + aVL + aVF = 0$  then the determination of the direction of

the various vectors becomes quite accurate. By the above reasoning one can determine the frontal plane projection of the mean spatial *QRS*, *ST* and *T* vectors and spatial *QRS*, *ST* and *T* loops.

After identifying the direction of the frontal plane projection of a spatial vector one then locates the transitional complex in the precordial leads. (A transitional complex is equally negative and positive or resultantly zero.) The transitional complex is recorded along the transitional pathway on the chest which is produced by a plane perpendicular to a spatial vector at its origin extended to the surface of the volume conductor. The location of this plane which is perpendicular to the spatial vector under study will therefore deter-

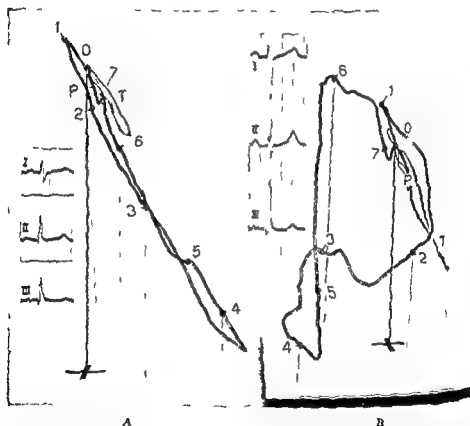


FIG. 48. (A) Photograph of wire loop representing the vectorcardiogram of a normal individual. The timing of the long obliquely placed *QRS* loop indicated by heavy black wire is shown by beads from 0 to 7 (time interval  $\approx 0.01$  second). The *P* loop is made of thin wire scarcely visible. The *T* loop is grey in color. The point of origin of all three loops *P*, *QRS* and *T* is zero. A black column supports the model. At the bottom of the stand a cross represents the normal axes of the body: the vertical bar the antero-posterior and the horizontal bar the transverse. The electrocardiogram (limb leads I, II and III) is shown at the left of the loop. (B) Wire loop representing the vectorcardiogram of a case of the tetralogy of Fallot with the graphs of the complexes and the electrocardiogram represented as in the case of A. (kindness of Dr. Pierre Duchosal, Geneva, Switzerland.)

mine the anterior or posterior displacement of a vector from the frontal plane thus identifying its spatial position. If the thorax is assumed to be a cylinder which is a reasonable assumption electrically speaking it is quite easy to visualize the transitional pathway and its relationship to the spatial vector. The method described allows one to determine the mean spatial vectors and by similar reasoning the spatial instantaneous vectors can be visualized. The range of error in determining the spatial direction of electrical forces approaches 15 degrees.

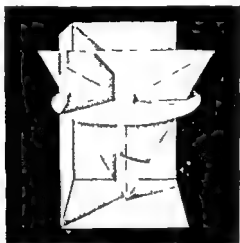


FIG 49 Drawing in perspective of the plans of derivations according to several systems. The rectangular trihedron symbolizes the derivations of the vector, the equilateral triangle that of the limbs, and the ellipse those of the precordium. (Kindness of Duchosal and Sulzer, Figure 43, page 111 of their book *La Vectocardiographie*, H. Karger, Bale and New York, 1949.)

In a general sort of way the *QRS* vector indicates the direction of the electrical field in the chest, and it becomes totally unnecessary to memorize various deflection contours in order to determine such a position. The spatial *QRS-T* angle is an extremely useful tool. It should be apparent that the *QRS* vector and *T* vector produce the sides of the parallelogram which is necessary to construct the ventricular gradient, and therefore the *QRS-T* angle incorporates certain of the properties of the gradient. The spatial *QRS-T* angle varies with age and in the normal adult is usually less than 60 degrees.

The electrocardiogram of a patient with a normal heart is shown analyzed by the vectorial method in Figure 50.

The electrocardiogram of a patient with an extensive anterior myocardial infarction is shown analyzed by the vectorial method in Figure 51.

**Electrocardiographic gradient.** Closely related to the cardiac vector and the electric axis is the so-called gradient, which may be calculated for either atria or ventricles, although to date attention has naturally been focused, as in other such studies, on the ventricles. The ventricular gradient, as defined by Burch

and Winsor (1949) is a vector expression (in quantitative terms) of the relative variations in duration of the excited state in the different portions of the ventricular musculature. Thus  $g$  (the ventricular  $g$ -gradient as projected on the frontal plane of the body) = the sum of  $A_{QRS}$  (the mean manifest magnitude of the QRS complex determined algebraically and measured in microvolt seconds or units *i.e.* the mean force of the depolarization process of the ventricular musculature) plus  $A_T$  (the mean manifest magnitude of the T wave which represents the repolarization process in microvolt seconds or units). The caret placed over the symbols indicates a vector value.

The technic of the measurement of the ventricular gradient consists of

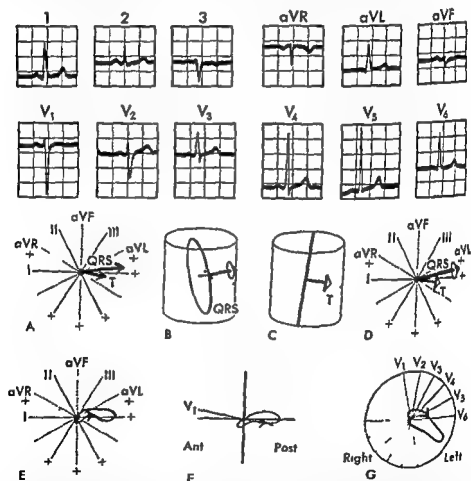


FIG 40 Thirty seven year-old normal male illustrating a horizontal position of the mean QRS vector (A) Mean QRS and T vectors as seen in the frontal plane (B) mean spatial QRS vector as seen in a cylindrical volume conductor (C) mean spatial T vector as seen in a cylindrical volume conductor (D) final "summary" figure to illustrate the spatial QRS and T electrical forces (E) frontal plane QRS loop (F) sagittal plane QRS loop and (G) coronal plane QRS loop seen from below (kindness of Dr J Willis Hurst Atlanta)

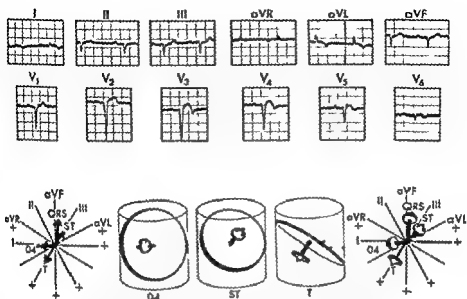


FIG 31 The electrocardiogram shown above is from a 50 year-old male with a characteristic history of myocardial infarction. The figure to the left shows a six axial lead arrangement which is produced by superimposing the unipolar extremity lead axes on the tri axial reference system of Bayley. This figure shows the frontal plane projection of the spatial QRS ST T and O4 vectors. Note that the mean QRS is only slightly positive in Lead I and is negative in Leads 2 and 3 and also fits the polarity of the unipolar extremity leads. The mean T vector is perpendicular to Lead aVR and therefore is largest in Lead 3. The mean ST vector is slightly negative in Lead aVR and the first O4 second of the QRS loop is approximately perpendicular to Lead aVF. The edge of the circular disc represents the transitional pathway along which transitional complexes will be recorded. The O4 second vector is tilted markedly posteriorly since the initial deflection is negative in Leads V<sub>1</sub> - V<sub>3</sub>. The ST vector is tilted markedly anteriorly since the ST segment is elevated in all the chest leads. The T vector is tilted only slightly anteriorly since the T wave is positive in Lead V<sub>1</sub> and negative in Leads V<sub>4</sub>, V<sub>5</sub>, V<sub>6</sub>. In general the O4 "dead zone vector" is directed away from an area of myocardial infarction and the T vector is directed away from the ischemic zone surrounding the area of infarction. The ST vector is directed toward the area of myocardial injury surrounding the area of infarction. The tracing above represents an extensive anterior myocardial infarction since the O4 vector is directed away from the anterior ventricular wall and the ST vector points toward the same area. The T vector is directed away from the lateral wall of the left ventricle. The diagram to the right illustrates how the spatial vectors are recorded routinely in clinical practice (Figure and legend through the kindness of Dr. J. Willis Hurst, Atlanta).

The O4 vector refers to the initial electrical force acting during the first O4 second of the QRS loop.

measuring the sum of the areas (A) in microvolt (one millionth volt) seconds under the QRS and T waves above the baseline in any two leads (preferably Leads 1 and 3) and subtracting the sum of areas below the baseline (Figure S2A). In the case of a single normal muscle strip (Figure S2B) the gradient would be zero since the depolarization area (R) above the baseline would be neutralized by the repolarization area (T) below the baseline. In human electrocardiography however the situation is very different there being many

heart muscle masses with varying individual influences per se and as affected by changes in position and rate of the heart as well as by disease. Thus since in the frontal plane the routine limb leads show normally preponderant upright *T* waves as well as preponderantly upright *QRS* waves the normal ventricular gradient in man has been found to average  $+52$  microvolt seconds or  $13.0$  units ( $1 \text{ unit} = 4 \text{ microvolt seconds}$ ) the range is not certain but has been put at a maximum of  $23.0$  units and a minimum of about  $2.5$  units (Burch and Winsor 1949). The gradient of *QRS* ( $A_{QRS}$ ) varies from about  $+12.0$  to about  $-3.5$  units. There is as yet little clinical applicability of the ventricular gradient although primary changes in  $A_T$  (i.e. not dependent on variations of the *QRS* wave) may be distinguished by this method.



FIG 52A Diagram showing the areas subtended by the *P* and *QRS* complexes and the area under the *T* wave. Areas above the isoelectric line are considered to be positive values and those below the isoelectric line are negative.

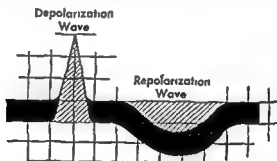


FIG 52B The process of depolarization and repolarization results in two separate waves which include areas of equal size (*A Primer of Electrocardiography* 2nd ed 1949 [1st ed 1945] kindness of Drs George Burch and Travis Winsor and Lea & Febiger Philadelphia).

## ELECTROCARDIOGRAPHIC COMPLEXES AND TIME INTERVALS

### THE ATRIAL DEFLECTION OR *P* WAVE

The normal *P* wave. Electrical activity of the atria is as a rule better defined and studied in Lead 2 than in the other routine leads because the axis of the *P* (atrial) wave is commonly parallel to Lead III for special analysis in difficult cases however the first precordial lead  $V_1$  may be useful or, best of all, a lead with electrode in the third interspace just to the right

of the sternum. Analysis of the normally inverted *P* wave in Lead aVR may also prove helpful.

The *P* wave of Lead 2 of the electrocardiogram is normally a blunt rounded sometimes slightly notched or scalloped upright deflection 1 to 3 mm high (each millimeter represents in a properly standardized record one tenth of a millivolt) and not over 0.1 second wide at the lower border of the baseline between corresponding points of upstroke and downstroke. This wave represents the spread of excitation over the atria along the muscle bundles from the normal starting point the pacemaker at the head of the sinoatrial node which lies at the junction of the superior vena cava and the right atrium (Figure 39 page 183). The atrial electric axis which is the resultant of the spread of current in all directions over the muscle of right and left atria is normally directed down and to the left in its projection on the anterior plane of the body which is that represented by the routine electrocardiogram. The *P* wave itself is very short in time interval and represents only about one third of the duration of atrial systole; it is followed however by a slight change in baseline of varying extent usually directed downward coinciding in time with the rest of the atrial systolic interval but as a rule concealed by the superimposition of the first ventricular complex or *QRS* wave. In heart block this late evidence of atrial electric activity may sometimes be clearly seen. It has been called the atrial *T* wave or *Ta* deflection (Figure 53).

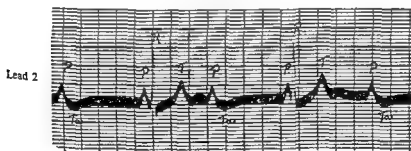


FIG 53 Electrocardiogram showing *Ta* waves in complete heart block. Lead 2.

The *P* wave of Leads 1 and 3. In Lead 1 the *P* wave is called  $P_1$ . It is of lower amplitude normally than in Lead 2; sometimes it is flat or isoelectric and so may be invisible; rarely it may be greater than the *P* wave in Lead 2 ( $P$ ). Normally when the *P* wave of Lead 3 ( $P_3$ ) happens to be inverted. Very rarely the *P* wave may be inverted in Lead 1 when there is normal rhythm; such a finding means congenital dextrocardia if an error has not been made in the attachment of the electrodes with resulting totally upside down Lead 1. When  $P_1$  is 2 mm or more in amplitude it is abnormal and the same factors responsible for an abnormally high or wide *P* are also responsible for too large a  $P_1$ . In other respects too the discussion about *P* applies to  $P_1$ .



In Lead 3 the *P* wave may normally be upright isoelectric diphasic or even slightly inverted. It is therefore the least desirable of the three bipolar limb leads for study of the atrial complex. However arrhythmias may be present in this lead and not in the others and one may also wish to note the character of the *P*<sub>3</sub> wave to aid in the interpretation of atrial abnormalities in the other leads and of the significance of inversion of *T*<sub>3</sub>.

In the *unipolar limb leads* the *P* wave like the *QRS* and *T* waves varies normally in direction and amplitude with the position of the heart. In the right arm lead (*aVR*) it is almost invariably inverted and often closely resembles except for its direction the *P* wave of Lead 2. In the left arm and left leg leads it is upright and of variable height higher in *aVL* than in *aVF* if the heart lies horizontally and vice versa if the heart is vertical.

In the *unipolar precordial leads* *V*<sub>1</sub> to *V*<sub>6</sub> inclusive, the *P* wave is not usually so well marked as in the limb leads. It may be of fair amplitude however and more often upright than otherwise in the first position just to the right of the sternum and when the right arm is used as the indifferent or distal lead point in general it may be upright, isoelectric diphasic or inverted.

**Abnormalities of the *P* wave.** The description of the *P* wave abnormalities herein refers in particular to Lead 2 which as a rule of the routine leads shows them best.

The *P* wave may show abnormalities of size and shape whether the heart rhythm is regular or not. Moreover the *P* wave itself may remain normal in some instances of irregular or disturbed rhythm as in heart block. Disorders of rhythm will be considered in the last three chapters of the book. Sinus arrhythmia however demands a brief discussion now.

Due to a variable activity of the pacemaker in the sinoatrial node caused by vagal influence and often associated with some bradycardia sinus arrhythmia (Figure 161 page 927) is generally a simple waxing and waning of rate with the intervals between normal *P* waves first decreasing and then increasing in phases related to the corresponding phases of respiration in inspiration and expiration. It is a normal phenomenon most common in children. If very marked or not related to respiration it is an abnormal phenomenon in which case digitalization or faulty coronary circulation or an unknown factor may be responsible. The *P* waves may decrease in amplitude with the periods of bradycardia as the pacemaker descends along the sinoatrial node usually they do not so decrease.

**Increase in amplitude (height) of the *P* wave** is usually associated with increase in its width or duration although one may be present without the other. An amplitude of 3 mm or more and a duration measured between corresponding points of upstroke and downstroke at the baseline of over 0.1 second are greater than the normal measurements in the subject at rest. Although exercise and sometimes increased sympathetic tone with tachycardia induced otherwise than by exercise tend to increase the height of the *P* wave even above the usual normal limit a constant increase in height or width or both of the *P* wave is most often found in three conditions namely mitral

stenosis and two congenital anomalies atrial septal defects and the tetralogy of Fallot both of which especially the first are associated with considerable atrial enlargement Hypertension especially with myocardial failure and less commonly other ill defined conditions may cause high *P* waves in the electrocardiogram When this atrial deflection is abnormally high or wide it tends also to be abnormally notched sometimes the notching is so deep that the deflection appears doubled Increased width of the *P* wave with or without increase in height is more likely to indicate enlargement of the left atrium as in mitral stenosis while preponderant increase in height with or without increase in width is more often found with enlargement of the right atrium as in the case of a congenital atrial septal defect

*Decrease in amplitude* may occur in vagal depression of the sinoatrial node with probable displacement of the pacemaker from the head of the node down toward the tail and this may be halfway or more along the sulcus terminalis toward the inferior vena cava This change in *P* wave may be seen to occur gradually or suddenly or it may be a constant finding it is frequently associated with a slowing of the heart rate It may sometimes be produced through vagal stimulation by pressure over the carotid sinus but it also may occur indirectly through the effect of digitalis or it may infrequently occur spontaneously as for example during the slowing of the heart rate at the end of expiration The clinical condition in which an abnormally low in fact often almost isoelectric or flat *P* wave is regularly found is hypothyroidism (Figure 92 page 454) due to either myxedema or cretinism This smallness of the *P* wave in such cases accompanies a tendency to low voltage throughout the electrocardiogram particularly involving the *T* wave When the clinical condition improves and the basal metabolic rate rises toward normal under treatment with thyroid gland the *P* wave also becomes more normal Under other varied circumstances the *P* wave is occasionally found very low the reasons for which are not clear Heart failure alone does not cause the change

*Absence of the P wave* as a separate definite deflection results from several causes (1) In the first place this is most commonly due to atrial fibrillation in which orderly sequence of atrial contraction is replaced by irregular rapid uncoordinated atrial movement (see Chapter 33) (2) In the second place the *P* wave may be replaced by regular instead of irregular baseline oscillations due to another condition closely related to atrial fibrillation namely atrial flutter (see Chapter 33) (3) In the third place the *P* wave may be partly or wholly buried in the *QRS* wave or in the *T* wave in cases of atrioventricular block (Figures 53 and 164 page 935) of paroxysmal tachycardia (Figures 156 and 157 pages 879 881) and of premature beats whether of atrial or ventricular origin (Figures 154 and 155 pages 868 869) of reciprocal rhythm or ventricular escape (Figure 161 page 927) and finally of the rare atrioventricular nodal rhythm (Figure 163 page 932) In most instances of these abnormal rhythms the *P* wave does not exactly coincide either with the *QRS* wave or with the *T* wave and so it can be distinguished A mechanical tracing of the jugular pulse may in some of the obscure cases reveal what is

going on by the presence or absence of the *a* wave superimposed on the *r* or on the *v* (4) Finally true atrial standstill or paralysis either transient or complete may account for the absence of the *P* waves due to depression of the pacemaker in the sinoatrial node and to inability of the lower, that is the atrioventricular node to start an atrial contraction (see Figure 162 page 979)

*Inversion of the P wave* (1) Inversion of the *P* wave in Lead 2 is abnormal and occurs most commonly in the case of atrial premature beats (see Figure 154) (2) Inverted or diphasic *P* waves also occur sometimes with continuous abnormal atrial rhythms most commonly in atrial paroxysmal tachycardia (Figure 156 page 879) (3) A third cause for inversion of the *P* wave is very much rarer than that due to atrial premature contractions or to atrial paroxysmal tachycardia is atrioventricular nodal rhythm already mentioned (see Figure 163) Rarely an excessive irritability of the atrioventricular junctional tissue may give rise to paroxysmal tachycardia originating there (4) A fourth cause of inversion of the *P* wave is retrogression giving rise to a so called retrograde *P* wave following a ventricular premature beat

In some instances the *P* waves are more readily studied otherwise than in Lead 2 for example in the special atrial lead with exploring electrode in the third intercostal space at the right sternal border or in an esophageal lead when the *P* waves are indistinct or not seen in other leads

### THE ATRIOVENTRICULAR OR *P R* (*P Q*) INTERVAL

The *P R* (*P Q*) interval is routinely studied in Lead 2 but observations of its length in the other leads should always be made It is a measure of atrioventricular conduction time from the atrial pacemaker through the atrial muscle across the junction from the atrial myocardium to atrioventricular node through this node and the bundle leading down from it and through the right and left bundle branches and their ramifications in the Purkinje net work into the ventricular muscle fibers themselves at which moment the *QRS* wave begins The *P R* interval is measured from the beginning of the upstroke of the *P* wave to the beginning of the *QRS* wave whether this be upstroke or downstroke It normally varies in the adult from 0.12 to 0.20 (or even in rare cases 0.21 or 0.22) second averaging 0.16 second and in infancy and childhood from 0.08 to 0.18 second averaging 0.12 or 0.13 second Its duration is undoubtedly a function of the heart size (Figure 53 page 207)

Some years ago it was demonstrated (White Leach and Foote 1941) that an error may arise in the measurement of the *P R* interval especially in Lead 2 due to the neutralization of *Q* and *R* waves in two of the three classical leads with resulting isoelectric onset of the *QRS* waves in the other lead thus apparently prolonging the *P R* interval This happens most commonly when a short *Q* or *R* in Lead 1 is exactly equal in amplitude and duration to a short *R* or *Q* in Lead 3 the *P R* interval in Lead 2 is then abnormally prolonged by 0.02 or 0.03 second to include the isoelectric onset of *QRS* Or

otherwise  $Q_1$  may neutralize  $Q$  to prolong  $PR_1$  or  $Q_2$  may neutralize  $Q$  to prolong  $PR_1$ . In occasional cases this error is clinically important when a  $PR$  interval of 0.19 or 0.20 second is read as 0.22 second. Hence careful scrutiny for this possible error is always essential. A factor less important, which may erroneously shorten the  $P$ - $R$  interval or neutralize the other effect, is an isoelectric beginning of the  $P$  wave.

**Lengthened  $PR$  interval** If the  $PR$  interval is over 0.21 second, atrioventricular block is said to be present. Only very rarely is a  $PR$  interval found to measure normally over 0.20 second, but in a few normal adults it has apparently even reached 0.22 second. The greater part of the  $PR$  time interval is consumed in the passage of the excitation wave through the atrioventricular node and the atrionodal junction just above it (see Chapter 34). The commonest causes of prolongation of the  $PR$  interval are active rheumatic myocarditis, coronary heart disease, and digitalis intoxication.

**Shortened  $PR$  interval** The  $PR$  interval may frequently appear shortened when the atria and ventricles are beating independently, as in complete heart block, reciprocal rhythm, or ventricular escape, and in many instances of the ventricular premature beat. In such cases it is better to speak of the intervals between the  $P$  waves and the  $R$  waves rather than of the  $PR$  interval as such. True shortening of the  $PR$  interval is found in atrioventricular nodal rhythm when the  $P$  wave, almost always inverted, falls just before, just after, or with the  $R$  wave, and in that variation of normal rhythm which consists of wide  $QRS$  waves with shortened  $PR$  intervals (of 0.1 second or less) in healthy young persons prone to paroxysmal tachycardia (Wolff, Parkinson, and White, 1930) (see Figure 168, page 953, and Chapter 34).

### THE FIRST VENTRICULAR DEFLECTION OR $QRS$ WAVE

**The normal  $QRS$  wave** The  $QRS$  wave, the first ventricular deflection of the electrocardiogram and sometimes called for short the  $R$  wave, is in Lead 2 a sharp spike-like monophasic, diphasic, or triphasic complex with little or no initial downward projection known as the  $Q$  wave, a high upward projection known as the  $R$  wave, and a variable, usually slight to moderate downward projection called the  $S$  wave (Figures 40, 42, 43, and 44). Together all components of the  $QRS$  complex should measure not over 0.1 second in duration. This first ventricular complex ( $QRS$  wave) represents the rapid activation of the entire ventricular myocardium by the excitation wave as it leaves the end branches (called the Purkinje fibers) of the special intraventricular conducting mechanism below the bundle of His. The terms dextrogram and levogram have been applied to records representing in experimental animals the primary spread of the excitation wave through right and left ventricles respectively; the addition of dextrogram and levogram results in the record obtained from both ventricles simultaneously. For the sake of convenience and uniformity it has been agreed generally to call the first upward deflection of the  $QRS$  wave the  $R$  phase or wave; any downward deflection

preceding the *R* the *Q* wave any downward deflection following the *R* the *S* wave and a second upward deflection following the *S* the *R* wave, if there is but one deflection downwardly directed it is labeled the *QS* wave (Committee of Electrocardiographic Nomenclature American Heart Association 1943) So far as time relations are concerned the *Q* of Lead 3 may coincide with the *R* of Lead 1 and the *R* of Lead 1 with the *S* of Lead 3 the nomenclature is not concerned with time relations but rather with direction above or below the baseline

The *Q* part of the *QRS* complex in Lead 2 is usually absent or at most but a short point projecting 1 or 2 mm below the baseline except in the case of infants and young children when it may form a more appreciable part of the whole *QRS* complex being as great as 3 or 4 mm in amplitude The *R* wave in Lead 2 in the normal adult varies from 5 to 35 mm in amplitude and in infants from 5 to 10 mm It is sharp rarely slightly notched or slurred on upstroke downstroke or peak It may be the only part of the *QRS* complex present The *S* wave is usually but a slight sharp downstroke of 1 to 3 mm immediately succeeding the *R* wave in fact continuous with it, it is frequently absent

In Leads 1 and 3 the *QRS* waves have normally less amplitude than in Lead 2 When the *R* or *S* wave occurs alone it is probable that either the other components are fused with it or they may be isoelectric and therefore invisible in one or another lead thus resulting in an erroneous measurement of the *QRS* duration A narrow *QRS* wave with isoelectric onset ending or both is most commonly found in Lead 2 where its apparent duration may in rare cases measure only half that of *QRS*<sub>1</sub> or *QRS*<sub>3</sub> an important error especially in the presence of bundle branch block which may be clearly evident in Leads 1 and 3 Thus all three leads must be carefully scrutinized not only to determine the correct measurement of the *P R* interval but also to learn the true *QRS* duration the widest *QRS* wave in any one of the three classical leads is the correct one and so as a rule, is the shortest *P R* interval Frequently in Lead 3 but rarely in Lead 1 the phase of the *QRS* wave with the greatest amplitude is normally directed downward whether *Q* or *S*

In the unipolar limb leads (Figures 42 43 and 44 pages 190 191 192) the *QRS* wave is normally inverted in Lead aVR with deep *Q* and small *R* usually upright but sometimes inverted (if the heart is very vertical) in Lead aVL and rarely normally inverted that is with *Q* wave in Lead aVF there may be very small *R* and *S* waves in Lead aVF if the heart lies horizontally

In the six unipolar precordial leads (*V*<sub>1</sub> to *V*<sub>6</sub> inclusive) the *QRS* wave is normally diphasic with short *R* and deep *S* in the first two leads and tall *R* and short *S* in the last two leads with *R* and *S* of intermediate amplitudes in Leads *V*<sub>3</sub> and *V*<sub>4</sub> in other words the *R* wave increases and the *S* wave decreases as one moves from right to left (see Figures 42 43 and 44 pages 190 191 192) It is to be noted that in the precordial leads the peak of the *R* wave marks the time of arrival of the intrinsic excitation wave at the muscle under

lying the particular exploring electrode involved the larger the ventricle the later and the higher the peak while the *S* wave usually reflects the activity of the opposite ventricle. *Q* waves normally are absent or small. Hence since the left ventricle is normally preponderant in size the *S* waves are larger over the right ventricle (that is in the right precordial leads) and the *R* waves are larger over the left precordial leads. However the position of the heart enters in and may cause on occasion a very confusing picture especially if we take into account rotation of the heart around each of its three axes (Goldberger 1947). The effects of these variations of position added to the effects of disease processes and of various physiologic and toxic states comprise an extremely complicated miscellany that will require much research completely to elucidate.

**Abnormalities of the *QRS* wave** The *precordial leads* may show the state of different parts of the heart in particular of the right and left ventricles better than do the limb leads since they reflect in the main what is directly beneath them. Thus if the right ventricle is enlarged there is a delay in the appearance of the intrinsic deflection represented by the peak of the *R* wave in Leads *V*<sub>1</sub> and *V*<sub>2</sub> overlying the right ventricle and along with this delay frequently an increase in amplitude also. If there is right bundle branch block the intrinsic deflection is still further delayed in those leads resulting in a wide bifid or M shaped complex. Also if the right ventricle is enlarged there tends to be a large *S* wave in the left precordial leads over the left ventricle that is in Leads *V*<sub>5</sub> and *V*<sub>6</sub>. Either Lead *V*<sub>3</sub> or *V*<sub>4</sub> is often a transitional point sometimes directly over the interventricular sulcus and sometimes over either ventricle and at right angles to the spatial axis as such either one is commonly used in identifying the anteroposterior plane in vectorcardiography (see page 202). In obscure cases x ray examination and the limb leads can help a good deal.

If the left ventricle is enlarged the *QRS* waves in Leads *V*<sub>1</sub> and *V*<sub>2</sub> are altered accordingly with delay in appearance of the peak of the *R* wave (intrinsic deflection) higher amplitude of the *R* wave and in Leads *V*<sub>5</sub> and *V*<sub>6</sub> over the right ventricle increased *S* waves. Here again displacement or rotation of the heart to the right gives much more evidence of the left ventricle in the precordial leads than usual and may be misleading. In left bundle branch block there is a much delayed intrinsic deflection peak in Leads *V*<sub>1</sub> and *V*<sub>2</sub> often giving an M shape.

The enlargement of the heart that affects the precordial *QRS* wave especially is that due to hypertrophy dilatation also has an effect on the duration of the *QRS* wave but manifests itself more on the *ST* segment and *T* wave because of the abnormal myocardial condition.

It is also important to note that normally the bigger the heart the wider the *QRS* wave without the need of postulating any abnormal delay in conduction. Thus the human infant's *QRS* wave is but 0.05 second wide normally the human adult's 0.10 second while the normal adult elephant's *QRS* wave is 0.20 second in duration (Figure 54) it would seem likely that the adult whale's *QRS* wave should be 0.4 second wide. Thus hypertrophy alone

undoubtedly gives rise to slightly increased *QRS* duration even up to 0.17 second without bundle branch block per se

Absence of the *R* wave leaving only a *QS* complex is an important residual effect of a myocardial infarct underlying the particular precordial lead concerned. This finding when present is a significant clue differentiating myocardial infarction from other conditions that may produce abnormal precordial *T* waves

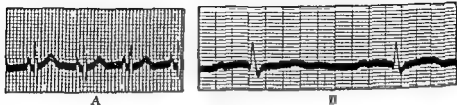


FIG 54 (A) Electrocardiogram (Lead 2) of a normal newborn infant BB showing the very short time intervals *P* *Q* *RS* and *Q* *T* (B) Electrocardiogram of a normal middle aged elephant M showing the very wide time relations a function of the size of the elephant's heart in contrast to the time intervals of the infant's electrocardiogram. The speed of the film is the same in both (A) and (B)

An important observation that should be added concerns the amplitude of the *QRS* wave in the precordial leads. Of equal importance with actual ventricular size is closeness of the lead to the heart. Thus a thin chest wall will result in greater amplitude while a thick (e.g. obese) chest wall or fluid will decrease the amplitude.

In the *unipolar limb leads* position of the heart is particularly reflected in the *QRS* waves as well as in heart disease. In general a deep *S* wave in Lead *aVR* goes with left ventricular preponderance and a horizontal heart position while a high *R* wave in Lead *aVF* goes with left ventricular preponderance and a vertical heart position. A *Q* wave is normally encountered but rarely in Lead *aVF* and an absence of *R* wave means a serious myocardial defect (an electrical hole facing the lead point usually due to infarction).

Finally in the old classical bipolar limb leads despite the concentration of interest in these leads in earlier editions of this book little can really be said about abnormalities of the *QRS* waves because of the wide range of the normal and the striking effect of varying positions of the heart. Thus the great bulk of instances of so called right and left axis deviations is of physiologic interest only associated primarily with heart position although there are cases of course, of extreme degree of really significant axis deviation as in the case of the tetralogy of Fallot or of the atrial septal defect. Also deep *Q* waves in Lead 1 are abnormal usually signifying anterior myocardial infarcts and especially prominent *Q* waves in Leads 2 and 3 generally mean posterior myocardial infarcts. And of course *QRS* waves over 0.12 second wide mean bundle branch block but it is not always so easy as we used to think to tell right from left branch blocks in these leads alone. There are exceptions that are properly revealed only in the precordial leads which should always be

taken anyway in cases with widened *QRS* waves. As a rule it is true that wide upright *QRS* waves in Lead 1 and wide inverted *QRS* waves in Lead 3 mean left bundle branch block, the reverse being true for right bundle branch block. The last chapter in the book will have more to say about this.

The term *low voltage* has been applied to the *QRS* wave in particular when it has extremely small amplitude either above or below the baseline. At one time 5 mm that is 0.05 mv was arbitrarily selected as the borderline of normal, inasmuch however as normal individuals have shown amplitudes either above or below the baseline of the limb leads of 4 to 5 mm (0.4 to 0.5 mv) it is better to restrict the term *low voltage* to amplitudes of the *QRS* wave of 3 mm (0.3 mv) or less, especially if the low voltage involves the *T* and *P* waves too. Such low voltage has been noted in several conditions, in particular in cases of diffuse myocardial disease due to coronary atherosclerosis or other cause, extensive pericarditis, acute or chronic, and rare factors as yet unexplained. In such cases the precordial leads generally show fair amplitude of the *QRS* waves but in a few instances they too may be much reduced and when they are the causative abnormal conditions are usually of greater degree. The voltage however of the *QRS* waves in the precordial leads is affected also by distance of the electrode from the heart. Thus an extensively fat chest wall or much fluid or air interposed between the heart and chest wall are factors that reduce the precordial *QRS* voltage.

*Alternation of the amplitude of the QRS waves* without other change (that is without alternating change of shape or of time interval) is exceedingly rare. I have seldom encountered it in the past 30 years. A few years ago two cases were reported, the first case being the only one found in a series of approximately 10,000 electrocardiograms taken over a period of 13 years (Hamburger, Katz and Saphir, 1936). The prognosis is apparently bad as in the case of the ordinary *pulsus alternans*. On the other hand, alternation of the arterial pulse is common and is attended in only the rarest cases by electrocardiographic alternation, either of *QRS* waves or *T* waves or both.

### THE *ST* SEGMENT

Immediately following the onset of systole that is after the *QRS* wave there is usually in the normal subject a short isoelectric interval showing itself electrocardiographically as the *ST* segment following the *ST* junction. Both the segment between the *S* and the *T* waves and that of the *T* wave itself are easily susceptible to modifying influences, physiologic effects, structural changes, anoxia, and myocardial infection and poisoning, which may produce changes of shape and amplitude. The *ST* segment and the *T* wave represent simply phases of the same electric process, repolarization during cardiac systole. The *ST* junction and *ST* segment may be normally slightly elevated up to 1 mm in limb leads and to 2 mm in precordial leads.

*Changes in the ST segment.* There are frequent changes in the *ST* segments which accompany abnormalities of the *T* waves themselves but which



actually may be more important in the information they yield about the myocardium they are as a rule temporary however subsiding when toxic influences and currents of injury subside. The most common and most striking *ST* segment abnormalities are those associated with digitalis intoxication and with myocardial infarction and ischemia (most commonly from coronary disease rarely from trauma or a state of vascular shock or anoxia) acute pericarditis with its associated subpericardial myocardial involvement may elevate the *ST* segments appreciably especially in Leads 1 and 2 and in the precordial leads involved. With full digitalization the *ST* segment of Leads 1, 2 and 3 and of the multiple precordial leads is considerably depressed and is said to sag, dropping sometimes several millimeters below the baseline so that the *T* may arise very low and be diphasic or in extreme cases totally inverted (see Chapter 30). This digitalis effect is in contradistinction to the findings in acute myocardial infarction and ischemia when the *ST* segments are depressed or raised from the baselines in the opposite direction to the *T* wave changes that is early in the anterior wall type of infarction the *ST* segment is elevated in Leads 1,  $V_4$  and  $V_5$  and depressed in Lead 3 and vice versa in posterior wall infarction type these changes are transient, persisting as a rule but a few hours or days (see Chapter 21). The *ST* segment tends to be markedly elevated in the multiple precordial leads over the region of the fresh anterior infarct while it may be considerably depressed in cases of acute posterior infarction (see Chapter 21). Also injury at the endocardial surface of the left ventricle may cause depression of the *ST* segments in the precordial leads over the left ventricle in contrast to the effect of the more usual subpericardial lesions. In the case of large chronic myocardial infarcts usually associated with cardiac aneurysms the *ST* segments may be permanently displaced (e.g. elevated in Leads 1,  $V_4$  and  $V_5$  in the case of large anterior aneurysms).

Infectious changes, other toxic poisoning of the myocardium and hyper-ventilation may sometimes affect the *ST* segment but rarely as much as does acute infarction or digitalization. Hypothyroidism has but little effect on the *ST* segment while flattening out the *T* waves. In some cases of left ventricular enlargement (or strain) there is a slight depression of the *ST* segment in Lead 1 even when there is no left axis deviation (Barnes 1940). In fact it is now well recognized that *ST* segment depression in Lead 1 and in Leads  $V_4$  and  $V_5$  is more characteristic of the effects of strain on the left ventricle than is left axis deviation; this simulates the effect of anoxia in acute coronary insufficiency.

### THE SECOND VENTRICULAR COMPLEX OR *T* WAVE

**The normal *T* wave.** The *T* wave or second ventricular wave of the normal electrocardiogram is in Lead 2 a blunt rounded upright deflection following the *ST* segment beginning gradually from the isoelectric baseline a short but variable distance about 0.05 to 0.15 second after the end of the *QRS* wave rising to a height of 2 to 10 mm usually 3 or 4 and sloping somewhat more

sharply downward to the baseline again to end about 0.25 to 0.30 second after the end of the normal QRS wave (Figures 42, 43, and 44). The duration or width of the T wave thus varies greatly from about 0.10 to 0.25 second. It falls during ventricular systole ending with the end of systole and the occurrence of the second heart sound. It has been variously explained, probably best as the repolarization (recharging) of the myocardium as contrasted with the depolarization (electric discharge) of the myocardium represented by the QRS wave. The T waves in Leads 1 and 3 are normally of less amplitude as a rule than the T wave.  $T_1$  is low (about 1 or 2 mm) but almost invariably upright normally while  $T_3$ , also of low amplitude, may be normally upright, flat, or even inverted. The T waves in the unipolar limb leads vary from normally inverted in aVR to upright or inverted in aVL and aVF depending on the position of the heart, tending to be inverted in aVL and upright in aVF in the case of a vertical heart and upright in aVL and low but not inverted in aVF in the case of a horizontal heart. The T wave in precordial Leads  $V_1$  to  $V_6$  inclusive is almost always upright (about 3 to 6 mm) in the normal adult but in the young child it may be inverted normally. The T waves vary from very low, flat, or inverted in  $V_1$  with increasing amplitude to high (5 to 10 mm) in  $V_3$  and  $V_4$  to lower levels in  $V_5$  and  $V_6$ ; they should not normally be inverted in the adult except in  $V_1$  and  $V_2$ .

*Physiologic variations of the T wave.* As stated above, the T waves in Lead 3 normally vary widely from upright to inverted depending in large part on position of the heart as affected by the height of the diaphragm in opposite phases of respiration and in opposite body builds; thus in full inspiration and in the case of a vertical heart the T waves in Lead 3 tend to be upright in direction with a swing of the electric (and anatomic) axis toward the right while in full expiration and in the case of a horizontal heart the T waves in Lead 3 tend to be inverted with a swing of the axis toward the left (see Figure 4, page 33).

Until recent years, however, flattening or inversion of the T waves in Leads 1, 2, and  $V_1$  to  $V_6$  in the adult has been attributed to actual heart disease. In Leads 1 and  $V_4$  and  $V_5$  such a surmise is almost invariably correct so far as we yet know, with very rare exceptions due to the same factors, namely heart position and autonomic nerve influences which can be responsible in the case of the far more numerous exceptions found in Lead 2.

Occasionally flattening, notching, or even inversion of the T waves in Lead 2 may be a positional effect in normal individuals; in such cases a vertical heart position in a long thorax with tendency to right axis deviation is attended in the sitting or standing position by notched, diphasic, or inverted T waves which assume the usual normal upright appearance in the recumbent position or on deep expiration (with or without much of any change in axis deviation of the QRS waves on changing position, rotation of the heart probably playing the important role). It is important to recognize this normal variation which has frequently in the past been attributed to myocardial disease (see Figures 5 and 6, page 34 and page 35) (White, Chamberlain, and Graybiel, 1941). In very rare cases even  $T_1$  may be normally inverted when the heart is

unusually placed vertically with the *T* in aVL deeper than in aVR or horizontally with marked clockwise rotation

In addition to the effect of position autonomic nerve impulses may affect the *T* waves in Lead 2. Sympathetic stimulation as during exercise and from fear or adrenaline and vagal inhibition as from atropine lower the *T* waves even to the point of inversion (Figure 55) (Hartwell et al 1942), while

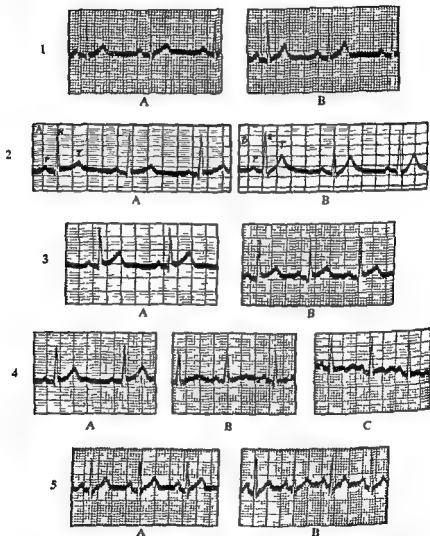


FIG 55 Changes in the *T* waves of the electrocardiogram resulting from the action of certain drugs in particular ergotamine atropine and adrenaline and of exercise (during and after). Note the increase in the *T* waves by vagus stimulation as evidenced by (1) the action of ergotamine and (2) the after-effect of exercise and the depression of the *T* waves as the result of sympathetic nerve stimulation or preponderance as evidenced by the effect of (3) atropine (4) adrenaline and (5) exercise itself directly. All tracings are of Lead 2 (A) control record (B) records at height of effect (C) shows maximal adrenaline effect—drug given intravenously (Hartwell Burrett Graybiel, and White *J Clin Investigation* 1942 XXI 403)

vagal stimulation as from ergotamine and *after exercise* raises the *T* waves (Figure 55)

**Abnormalities of the *T* wave** *Increase in amplitude of the *T* wave* The end of the *T* wave of Lead 1 tends to become higher in cases of posterior myocardial infarction due to coronary thrombosis in contrast to late inversion of the *T* wave in Lead 3 while the reverse is true that is there is a late increased elevation of  $T_3$  when there is late inversion of  $T_1$  in the cases of anterior wall infarction In the old Lead 4 and in the multiple precordial leads over the left ventricle  $V_4$ ,  $V_5$  and  $V_6$  the *T* may remain unchanged or become higher than normal in the posterior wall infarction it is almost always considerably inverted in the anterior wall infarction (see Chapter 21) especially in chest Leads  $V_4$ ,  $V_5$  and  $V_6$  In cases of lateral wall infarction it may be inverted in Lead  $V_6$  only

In the electrocardiograms of premature beats marked axis deviation and bundle branch block the *ST* segment and *T* wave are usually widely deviated from the baseline in the opposite direction from that of the abnormal *QRS* wave thus giving sometimes very high *T* waves A similar opposite direction of *T* wave from *QRS* wave in Leads 1 and 3 helps to separate the marked axis deviation due to pathologic cardiac conditions from left axis deviation of lesser degree which may be due to change in position of the heart (when the *T* wave tends to take the same direction from the baseline as does the *QRS* wave) Thyrotoxicosis sometimes stated to show a *T* wave increase is as a matter of fact generally without appreciable effect or has an opposite effect even to flatten or invert the *T* wave doubtless due to the sympathetic overstimulation

*Decrease in amplitude and inversion of the *T* wave* Decrease in amplitude of the *T* waves from the normal and their inversion in disease are found under several conditions In Lead 2 decrease in amplitude is frequently present in marked left or right axis deviation or even in right or left bundle branch block along with a diphasic character of the *QRS* wave due to the neutralizing effect of Leads 1 and 3 on each other In general however flattening and inversion of the *T* waves in the three classical leads are most commonly the result of digitalis action of myocardial ischemia or infarction from coronary disease of acute pericarditis or chronic constrictive pericarditis of infectious myocardial involvement and of hypothyroidism (myxedema or cretinism) There are differences between the effects of these five clinical conditions In the multiple precordial leads the *T* waves vary according to the part of the heart affected but are influenced like the limb leads by general factors such as digitalis myocarditis and myxedema

1 Digitalization usually causes a decrease leading to flattening or even in extreme cases to deep inversion of the *T* wave following a sagging of the *ST* segment (see Figure 158 page 897 and Chapter 30)

2 The *T* wave of myocardial ischemia or infarction due to coronary disease or insufficiency tends to be flattened or inverted in Lead 2 but varies in the other leads according to the site of the maximum amount of myocardial

change. It is at first slightly elevated along with the *ST* segment, in Lead 1 with or without very slight late inversion (Pardee's sign Pardee 1920) during the most acute stage of anterior wall type of myocardial infarction (due probably to a current of injury at the left ventricular apex) but it becomes usually sharply inverted after a few days remaining inverted for weeks, months or years. When there is chronic coronary insufficiency with or without actual old infarction involving a large area of the left ventricle toward the apex the *T* waves in Leads 1 and  $V_4$  and  $V_5$  are usually flattened or inverted in their terminal portions. In cases of anterior wall myocardial infarction or left ventricular basal ischemia the same statements just made concerning  $T_1$  apply to the *T* waves in Lead 3 instead. In the multiple precordial leads the *T* waves are unchanged or heightened in the case of the posterior wall infarction or left basal ischemia and flattened or inverted (often deeply so) over the left ventricle in the case of anterior infarction or left apical ischemia. When there are multiple areas of infarction or ischemia there are multiple effects on the electrocardiogram which are often confusing perhaps the simplest combination is inversion of the *T* waves in Leads 1, 2 and 3 with diphasic *T* waves in the precordial leads over the left ventricle when there are comparable infarcts at both apex and base (see Chapter 21).

In the multiple precordial leads inversion of the *T* waves over the right side of the precordium and not over the left indicate enlargement of or damage to the right ventricle or infarction of the interventricular septum while inversion of the *T* waves over the extreme left side of the precordium indicate infarction or other damage of the lateral wall of the left ventricle.

3 With pericarditis especially when there is acute or chronic constriction of the heart and great vessels the *T* waves tend to become flattened or more often inverted in all leads after temporary elevation of the *ST* segments but especially in Leads 1 and 2 for some days in the early stages (see Chapter 27).

4 With serious infections there are occasionally observed changes in the *T* waves consisting of decrease in amplitude flattening or inversion in both limb leads and multiple precordial leads similar to those just recounted as sometimes occurring in pericarditis these changes are due to acute myocardial involvement and are particularly likely to occur in rheumatic fever, diphtheria and pneumonia and sometimes in virus diseases. The same effects are due rarely to noninfectious poisons (other than digitals which has been mentioned above) as from tobacco (see Chapter 23).

5 The *T* waves of hypothyroidism are very low, absolutely flat (most commonly) or even inverted in all leads they resume a normal amplitude after thyroid therapy (see Chapter 18).

There are other rare instances of depression or inversion of the *T* waves of uncertain or unknown nature and even an individual who is apparently normal may temporarily show this finding due as a rule to unusual heart position or nerve influence (see Figures 5 page 34 and 55 page 218 for example).

The *T* wave is frequently diphasic but rarely notched. Its diphasic character results often from the inverted nature of the *S-T* segment which merges into the slightly upright *T* wave as in digitalis action; occasionally the diphasic sequence is the reverse—first upright then inverted as in cases of cardiac infarction. A late notch or dip in a low *T* wave in Lead 2 suggests the effect of heart position in an otherwise normal person in the sitting position; in such a case a further electrocardiogram should be taken with the subject recumbent or in full expiration to correct the effect of the heart's unusual angle or rotation.

Alternation of the *T* waves in amplitude alone like alternation of the *QRS* waves is very rare; it may accompany alternation of the arterial pulse as a serious sign.

### THE *Q-T* DURATION

The time interval from the onset of the *QRS* wave to the end of the *T* wave can be taken to measure quite accurately the duration of ventricular systole when the deflections are clearly marked so that the end points are readily seen. With good technique this so-called *Q-T* duration of the electrocardiogram is the best measure we possess for the length of systole. With clear curves measurement by the Lucas comparator gives an error under 0.01 second. The *Q-T* duration (duration of systole) varies primarily with the heart rate being shorter with faster rates and longer with slower rates: about 0.35 second at a heart rate of 75, 0.25 second at a rate of 120 and 0.45 second at a rate of 45. The *Q-T* duration varies abnormally only in some cases with high grade atrioventricular and intraventricular block, in ventricular premature beats, in hypocalcemia and hypopotassemia, and with marked enlargement (especially dilatation) of the heart, in which conditions it is longer than the outer limit of the normal. In heart failure a prolonged *Q-T* duration (systole) is shortened by an adequate digitalis effect. With respect to heart size it is of considerable interest that the duration of systole (the *Q-T* duration) of the elephant's heart is relative to heart rate much longer than that of the human heart (White, Jenks and Benedict 1938) (Figure 54, page 214) and one might justly prophesy that the whale's *Q-T* duration like other time intervals would be similarly relatively prolonged.

### THE *U* WAVE

Occasionally in Leads 1 and 2 and frequently in the precordial leads there occurs normally a slight upright deflection, a small wave usually less than 1 mm high but sometimes higher immediately following the *T* wave and therefore appearing in early diastole (Figures 40, 42, 44 and 53). This is called the *U* wave. Its significance is unknown but it is probably representative of some diastolic electric process in the myocardium since it is more evident after a high or deep *T* wave than at other times and since it tends to be inverted when the *T* wave is inverted. The *U* wave is apparently of little clinical

importance except that it may be abnormally inverted when the *T* wave is upright and that it may be confused with the *P* wave or more commonly with the end of the *T* wave in which latter case it may be wrongly interpreted as a notching of the *T* such an error can be avoided by a measurement of the expected *Q-T* interval at the heart rate recorded

**Serial electrocardiograms** In closing this chapter I would like to emphasize the great importance of serial electrocardiography. Repeated records are often essential for the diagnosis of such acute conditions as myocardial infarction, acute pericarditis and the acute cor pulmonale. Annual, monthly, weekly, daily or even hourly records may reveal much more than any single electrocardiogram. Also every young person while in good health should have a routine electrocardiogram taken for future reference just as he or she should also have a chest x ray film.

## BIBLIOGRAPHY

### ELECTROCARDIOGRAPHY

SEE ALSO REFERENCES UNDER CHAPTER 12 TO 20 INCLUSIVE AND FOLLOWING CHAPTERS 31. PREMATURE BEATS AND PAROXYSMAL TACHYCARDIA 32. ATRIAL FIBRILLATION AND ATRIAL FLUTTER. QUINIDINE THERAPY AND 33. HEART BLOCK.

- American Heart Association. Second Supplementary Report by the Committee for the Standardization of Precordial Leads. *Am Heart J* 1943 XXV 535
- Ashman R. and Byer E. "The Normal Human Ventricular Gradient I. Factors Which Affect Its Direction and Its Relation to the Mean QRS Axis." *Am Heart J* 1943 XXV 16
- II. Factors Which Affect Its Manifest Area and Its Relationship to the Manifest Area of the QRS Complex. *Ibid* 1943 XXV 36
- Ashman R. and Hull E. *Essentials of Electrocardiography*. Macmillan Co. New York. 2nd ed. 1941 (1st ed. 1937)
- Barker P. S., Macleod A. G., Alexander J. and Wilson F. M. "The Excitatory Process Observed in the Exposed Human Heart." *Tr A Am Physicians* 1939 XLIV 125 and *Am Heart J* 1930 V 720
- Barnes A. R. *Electrocardiographic Patterns Their Diagnostic and Clinical Significance*. Charles C. Thomas Publisher Springfield Ill. 1940
- Bayliss W. M. and Starling E. H. "On the Electromotive Phenomena of the Mammalian Heart." *Internat Monatsschr f Anat u Physiol* 1892 IX 256
- Bernstein P. and Mann H. "Clinical Evaluation of Fetal Electrocardiography. Study of 100 Cases by New Technique and Improved Instrument." *Am J Obst & Gynec* 1942 XLIII 21
- Carter E. P., Richter C. P. and Greene C. H. "A Graphic Application of the Principle of the Equilateral Triangle for Determining the Direction of the Electrical Axis of the Heart in the Human Electrocardiogram." *Bull Johns Hopkins Hosp* 1919 XXV 16
- Cohn A. E., Fraser F. R. and Jamieson R. A. "The Influence of Digitalis on the T Wave of the Human Electrocardiogram." *J Exper Med* 1915 XXI 493
- Craib W. H. *The Electrocardiogram*. Medical Research Council Special Report Series No 147. London 1930
- Einthoven W. "Ein neues Galvanometer." *Annalen der Physik Folge IV* 1903 VII 1059

- Einthoven W, Fahr G and de Waart A "On the Direction and Manifest Size of the Variations of Potential in the Human Heart and on the Influence of the Position of the Heart on the Form of the Electrocardiogram" *Pflügers Arch f d ges Physiol* 1913 CL 275 Translated by Hoff H E and Sekelj P *Am Heart J* 1950 XI 163
- Feil, H "The Auricular Wave (P) of the Human Electrocardiogram in Normal and Pathological States" *J Mt Sinai Hosp* 1942 VIII 502
- Frieleria L ■ Die Systolendauer im Elektrokardiogramm bei normalen Menschen und bei Herzkranken I Beziehung zwischen der Pulsfrequenz und der Dauer des Ventrikelelektrokardiogramms bei normalen Menschen in der Ruhe *Acta med Scandinav* 1920-21 LIII 469
- Galvani L *De viribus electricitatis in motu musculari commentarius* Istituto delle scienze di Bologna 1791 VII
- Goodyer A V N, Geiger A J and Monroe W M Clinical Fetal Electrocardiography *Yale J Biol & Med* 1942 XV 1
- Hamburger W W, Katz L N and Saphir O Electrical Alternans A Clinical Study with a Report of Two Necropsies *JAMA* 1936 CVI 902
- Hartwell A S, Burrett, J B, Graybiel A and White P D "The Effect of Exercise and of Four Commonly Used Drugs on the Normal Human Electrocardiogram with Particular Reference to T Wave Changes" *J Clin Investigation* 1942 XXI 409
- Recht H H "The Influence of the Indifferent Electrode Upon the Precordial Electrocardiogram" *Am Heart J* 1942 XXIV 529
- Herrmann G and Schwab E H Some Experimental and Clinical Electrocardiographic Observations on R S T and T Changes in Pericarditis *Tr A Am Physicians* 1934 XLIX 229
- Katz L N *Electrocardiography* Lea & Febiger Philadelphia 1941
- Exercises in Electrocardiographic Interpretation* Lea & Febiger Philadelphia 1941
- Katz, L N et al "The Diagnostic Value of the Electrocardiogram Based on the Analysis of 149 Autopsy Cases" *Am Heart J* 1942 XXIV 627
- Kisch B, Nahum L H and Hoff H E "The Predominance of Surface Over Deep Cardiac Injury in Producing Changes in the Electrocardiogram" *Am Heart J* 1940 XX 174
- Kolliker A and Müller H "Nachweis der negativen Schwankung des Muskelstroms am natürlich sich contrahierenden Muskel" *Verhandl d physik med Gesellsch* 1856 VI 528
- Kraus F and Nicolai G *Das Elektrokardiogramm des gesunden und kranken Menschen* Viet Leipzig 1910
- Lewis T *The Mechanism and Graphic Registration of the Heart Beat* Shaw and Sons Ltd London 3rd ed 1925 (1st ed 1911)
- Mainzer F and Krause M "The Influence of Fear on the Electrocardiogram" *Brit Heart J* 1940 II 221
- Mann H A Method of Analyzing the Electrocardiogram *Arch Int Med* 1920 XXV 283
- "The Monocardiograph" *Am Heart J* 1938 XV 681
- Marcel M P and Exchaquet J P L electrocardiogramme du fœtus humain *Arch d mal d coeur* 1938 XXXI 504
- Matteucci C Sur le courant électrique des muscles des animaux vivantes ou récemment tués *Compt rend d Acad d sc* 1843 XVI 197
- Nahum L H and Hoff H E "The Interpretation of the U Wave of the Electrocardiogram" *Am Heart J* 1939 XVII 585
- Pardé H E ■ An Electrocardiographic Sign of Coronary Artery Obstruction" *Arch Int Med* 1920 XXVI 244
- Clinical Aspects of the Electrocardiogram* Paul H Hoeber Inc New York 4th ed 1941 (1st ed 1924)
- Parkinson, J and Bedford D E Successive Changes in the Electrocardiogram After Cardiac Infarction (Coronary Thrombosis) *Heart* 1928 XIV 195
- Rykert H E and Hepburn J "Electrocardiographic Abnormalities Characteristic of Certain Cases of Arterial Hypertension" *Am Heart J* 1935 X, 937
- Samojloff A and Steshinsky M Ueber die Vorhoferhebung des Elektrokardiogramms bei Mitralklappenstenose *Munch med Wchnschr* 1909 LVI 1942



- Sanderson J B and Page F J M On the Time Relations of the Excitatory Process in the Ventricle of the Heart of the Frog *J Physiol* 1880 II 384
- Sigler L Electrocardiographic Changes with Alterations of Posture from Recumbent to Standing Positions *Am Heart J* 1938 XV 146
- Smith F M "The Ligation of Coronary Arteries with Electrocardiographic Study" *Arch Int Med* 1918 XXII 8
- Waller A D A Demonstration on Man of Electromotive Changes Accompanying the Heart's Beat *J Physiol* 1887 VIII 229
- White P D Chamberlain F L and Graybiel A Inversion of the T Waves in Lead II Caused by a Variation in Position of the Heart *Brit Heart J* 1941 III 253
- White P D Jenks J L Jr and Benedict F G The Electrocardiogram of the Elephant *Am Heart J* 1938 XVI 744
- White P D Leach C E and Foote S A "Errors in Measurement of the P R (P-Q) Interval and QRS Duration in the Electrocardiogram" *Am Heart J* 1941 XXII 311
- White P D and Mudd E G Observations on the Effect of Various Factors on the Duration of the Electrical Systole of the Heart as Indicated by the Length of the Q-T Interval of the Electrocardiogram *J Clin Investigation* 1929 VII 387
- Wilson F N "The Distribution of the Potential Differences Produced by the Heart Beat Within the Body and at Its Surface" *Am Heart J* 1930 V 599
- Wilson F N Macleod A G and Barker P S *The Distribution of the Currents of Action and of Injury Displayed by Heart Muscle and Other Excitable Tissues* University of Michigan Press Ann Arbor 1933
- Wise N B Comeau W J and White P D "An Electrocardiographic Study of Twins" *Am Heart J* 1939 XVII 701
- Wolff L Parkinson J and White P D Bundle Branch Block with Short P R Interval in Healthy Young People Prone to Paroxysmal Tachycardia *Am Heart J* 1930 V 685
- Wood F C and Wolferth C C An Electrocardiographic Study of Coronary Occlusion The Inadequacy of the Three Conventional Leads in Recording Certain Characteristic Changes in Action Currents *J Clin Investigation* 1932 XI 815

#### Recent References (1944-1950)

- Abildskov J A Burch G E and Cronin J A The Validity of the Equilateral Tetrahedron as a Spatial Reference System *Circulation* 1950 II 122
- Bayley R H The Electrocardiographic Effects of Injury at the Endocardial Surface of the Left Ventricle *Am Heart J* 1946 XXXI 677
- Benjamin J M Jr Schwan H Kay C F and Hafkenschiel J H The Electrical Conductivity of Living Tissues As It Pertains to Electrocardiography I Review of the Problem of Homogeneity vs Nonhomogeneity an Outline of the Technical Aspects of Tissue Resistivity Measurements and a Critical and Experimental Analysis of Certain Pertinent Experiments" *Circulation* 1950 II 321
- Burch G E and Winsor T A *Trimer of Electrocardiography* Lea & Febiger Philadelphia 2nd ed 1949 (1st ed 1945)
- Dressler W and Roesler H *An Atlas of Electrocardiography* Charles C Thomas Publisher Springfield Ill 1949
- Duchosal P and Sulzer R *La Vectorcardiographie* Karger Bale (Suisse) 1949
- Franke H and Gebert E Über die asynchrone Erregung der Vorhöfe im intrakardialen Ekg beim gesunden Organismus" *Ztschr f Kreislauff* 1950 XXIX 513
- Goldberger E "An Interpretation of Axis Deviation and Ventricular Hypertrophy" *Am Heart J* 1944 XXVIII 621
- "The Validity of the Einthoven Triangle Hypothesis" *Am Heart J* 1945 XXIX 369
- Unipolar Lead Electrocardiography* Lea & Febiger Philadelphia 1947
- Goldman S Vivian W E Chien C K and Bowes H N "Electronic Mapping of the Activity of the Heart and the Brain" *Science* 1948 CVIII 720
- Grant R P "An Approach to the Spatial Electrocardiogram" *Am Heart J* 1950 XXXIX 17
- Grant R P and Estes E H *The Interpretation of the Electrocardiogram by Vector Methods* Blakiston Co., Philadelphia and Toronto 1951

- Graybiel A, McFarland R, A, Gates D C and Webster F A "Analysis of the Electrocardiograms Obtained from 1000 Young Healthy Aviators" *Am Heart J*, 1944 XXVII 524
- Graybiel A and White P D *Electrocardiography in Practice* W B Saunders Co Philadelphia, 2nd ed 1946 (1st ed 1941)
- Grewin, K E *Some Supplementary Leads in Clinical Electrocardiography with Special Regard to Electrode Placement Normal Range and Routine Applicability of Certain Chest Leads* Ivar Haeggströms Boktryckeri AB Stockholm 1948
- Hecht H H "Potential Variations of the Right Auricular and Ventricular Cavities in Man." *Am Heart J* 1946 XXXII 39
- Hein E and Reavis J C "Direct Electrocardiograms from the Human Heart in Situ Direct Leads with Precordial Leads" *Circulation* 1950 I 964
- Holter N J and Gengerelli J A "Remote Recording of Physiological Data by Radio" *Rocky Mountain M J* 1949 XLVI 747
- Hunzicker W J and Levine H D "Clinical Evaluation of Direct Writing Electrocardiography" *Am J Med Sc* 1949 CCXVIII 37
- Hurst J W and Doyle J T *Atlas of Electrocardiography* In press 1951
- Kanatsoulis A "Télé electrocardiographie" I *Congrès Mondial de Cardiologie Paris* Sept 3-9 1950 J B Bailliere et Fils 1950
- Kustin, A D Brill W D and Robb G P "Normal Esophageal and Gastric Electrocardiograms Description Statistical Analysis and Bearing on Theories of Electrocardiographic Position" *Circulation* 1950 II 578
- Langner P H Jr and Atkins J P "Intrabronchial Electrocardiography A Preliminary Report" *Circulation* 1950 II 419
- Leclercq J and Maurice P "La dérivation directe intracavitaire des courants électriques de l'oreillette et du ventricule droits" *Paris med* 1945 XXXV 23 and *Arch d mal d coeur* 1945 XXXVIII 298
- Lepeschkin M "Zur Standardisierung der Brustwandableitungen des Ekg" *Ztschr f Kreislauff* 1949 XXXVIII 9
- Electrocardiographic Observations on the Mechanism of the Electrical Alternans of the Heart *Cardiologia* 1950 XVI 178
- Levine H D Hellemis H A, Wittenborg M H and Dexter L "Studies in Intracardiac Electrography in Man I The Potential Variation in the Right Atrium" *Am Heart J* 1949 XXXVII 46
- Levine H D Hellemis H A, Dexter L and Tucker A S II "The Potential Variations in the Right Ventricle" *Am Heart J* 1949 XXXVII 64
- Littmann D "Abnormal Electrocardiograms in Absence of Demonstrable Heart Disease" *Am J Med* 1948 V 337
- Myers G B "The Form of the QRS Complex in the Normal Precordial Electrocardiogram and in Ventricular Hypertrophy" *Am Heart J* 1950 XXXIX 637
- Myers G B and Klein, H A "The Relation of Unipolar Limb Leads to Precordial and Esophageal Leads" *Am Heart J* 1948 XXXV 727
- Roseman J F P Q R S T *A Guide to Electrocardiogram Interpretation* Macmillan Co New York 2nd ed 1947 (1st ed 1944)
- Sodi Palares D *Nuevas Bases de la Electrocardiografía* Edición del Inst Nacional de Cardiología de México 2nd ed 1949 (1st ed 1945)
- Stewart C B and Manning, G W "A Detailed Analysis of the Electrocardiograms of 500 RCAF Aircrew" *Am Heart J* 1944 XXVII 502
- Wilson F N et al "The Precordial Electrocardiogram" *Am Heart J* 1944 XXVII 19
- "The Substitution of a Tetrahedron for the Einthoven Triangle" *Am Heart J* 1947 XXXIII 594
- Wolferth C C and Livezey M N "A Study of Methods of Making So-Called Unipolar Electrocardiograms" *Am Heart J* 1944 XXVII 764
- Wolff L *Electrocardiography Fundamentals and Clinical Application* W B Saunders Co Philadelphia 1950
- Wosika P H, Feldman E, Chestow E J and Myers G B "Unipolar Precordial and Limb Lead Electrocardiograms in the Aged" *Geriatrics* 1950 V 131

# OTHER METHODS OF EXAMINATION

---

### INTRODUCTION

The patient's history, physical examination, electrocardiogram, and roentgen ray study have been discussed in the earlier chapters of this book and have been roughly appraised in value as parts of the complete clinical examination in the order of about 45, 25, 15, and 10 per cent respectively. These percentages add up to 95, leaving the remaining 5 per cent to be divided up among all the other methods of examination which include the technic of cardiac catheterization and the testing of blood, urine, strength and endurance, vital capacity, and other respiratory functions, blood flow, circulation rate, and work of the heart and of the pulse. Various other tests of less immediate or routine cardiovascular importance, such as the basal metabolic rate and sputum and gastrointestinal examinations, are not included in this chapter but are referred to later in appropriate chapters. Any one of these methods of examination may, however, uncover a vital clue, and so they must all be borne in mind and turned to at once in case of need. Many of the additional tests, such as ballistocardiography, the discussion of which has been transferred to a more appropriate chapter (Chapter 8), are of much academic interest and worthy of use in special investigations; a few may some day assume practical importance in clinical medicine related to the heart and great vessels. As a whole, however, at the present time the methods discussed in this chapter are infrequently of prime importance in cardiovascular diagnosis, although they may be invaluable in the execution of special research.

### CARDIAC CATHETERIZATION

Forssmann, W. "Die Sondierung des rechten Herzens" (Sounding the Right Heart") *Min Wchnschr* 1928 VIII 2085\*.

\* Shortly after the publication of this paper Dr. Forssmann's attention was called to an earlier publication on catheterization of arm veins in the human for the purpose of therapy (Bleichroder, Unge, and Loeb, "Intraarterielle Therapie" *B I Min Wchnschr* 1911, 1) II. However, this earlier work apparently did not include catheterization of the heart per se and was not followed up by further research or application.

Following the successful investigations in the cadaver I undertook the first study in living man in the form of a *research on myself*. Next I arranged in a preliminary test to have my right elbow vein punctured with a thick needle by a colleague who kindly placed himself at my disposition for this purpose. I introduced then as in the case of the researches on the cadaver a well oiled ureteral catheter of 4 Charrieres thickness through a cannula into the vein. The catheter allowed itself to be introduced very easily to a length of 35 cm. Since going further seemed too dangerous to the colleague we stopped the investigation at that point even though I myself felt quite well. After a week I undertook a further investigation alone. Since a puncture of the vein with a thick needle on my own body was technically too difficult I made under local anesthesia a venesection in my left elbow and introduced the catheter without any resistance in its whole extent of 65 cm. This length appeared to me after measuring the surface of the body to agree with the distance from the left elbow to the heart. On introduction of the catheter I had during the procedure merely a feeling of slight warmth in the wall of the vein similar to the sensation after intravenous injection of calcium chloride. On backward movement the catheter touched the upper and lower wall of the subclavian vein. I then felt an especially intensive warmth behind the collar bone under the insertion of the sternocleidomastoid. Simultaneously doubtless through the stimulation of the vagus branches I felt a slight tendency to cough.

The position of the catheter I confirmed in a Rontgen photograph and observed the shadow of the catheter itself by means of a mirror held by a sister before the fluoroscopic screen. (Translation by myself.)

Thus in 1929 Forssman successfully catheterized his own heart by way of an arm vein. Considered a bold and dangerous procedure at first it has in the last few years become a commonplace though still a delicate method of study of the right heart chambers and pulmonary arterial circulation particularly in congenital cardiovascular disease and in measurement of the pulmonary blood pressure a longfelt want now at last realized (Figure 56). It is very important wherever cardiac catheterization is carried out to establish a well trained team of workers to ensure proper technic and adequate recording such a team usefully includes cardiologist roentgenologist cardiovascular surgeon and physiologic technician. It is well to record the blood pressure in the superior vena cava in the right atrium in the right ventricle and in the pulmonary artery and its main branches by Hamilton manometer or by the newly introduced *electromanometer* (see Chapter 6). Samples of blood for determination of oxygen content are taken similarly from these various sources to determine if possible the entrance of oxygenated blood through atrial septal defect ventricular septal defect or patent ductus arteriosus (see Chapter 13). The course of the specially modified ureteral catheter 100 to 125 cm in length can be followed fluoroscopically as it passes from one chamber to another or in abnormal hearts into left atrium or aorta and x ray films can occasionally be taken. It is possible also to use such a catheter to explore

---

Also Forssmann mentioned the fact that Christeller and Eisner had used Ungers arterial method in animal experimentation. Forssmann refers to these two earlier communications in a short statement in the *Klin Wchnchr* 19 9 VIII 787.



FIG 56 X ray films of thoraces with catheter in heart (A) Normal heart Catheter is seen entering the right atrium from the superior vena cava and its tip can be noted in the right pulmonary artery (B) Atrial septal defect with pulmonary stenosis The catheter is seen to pass from the right atrium through the septal defect in the left atrium and into a right pulmonary vein Note the lower position of the pulmonary vein in contrast to that of the artery



C



D

(C) Large patent ductus arteriosus. The catheter is seen to pass from the main pulmonary artery through the ductus and down the descending aorta. (D) Tetralogy of Fallot. The aortic arch is right-sided. The catheter is seen entering the aorta from the right ventricle. (Kindness of Drs. Gordon S. Myers, Massachusetts General Hospital, Boston; Bernard J. Walsh, Washington D.C.; and Lewis Dettler, Peter Bent Brigham Hospital, Boston.)

the coronary hepatic and renal veins and determine blood gases to study local organ metabolism. Finally it is possible by the insertion of a special wire and electrode through the catheter to obtain right intra atrial and intraventricular electrocardiograms which as yet have been largely of academic interest (see Chapter 9)

In normal individuals the blood pressure in the superior vena cava has been found to be about 3 mm Hg in the right atrium 0 in the right ventricle 20 to 30 mm systolic and 0 diastolic and in the pulmonary artery 20 to 30 mm systolic and 5 to 10 mm diastolic. With the catheter tip as far as possible in the pulmonary vessels an essentially capillary oxygen reading can be secured.

The oxygen content of blood samples taken from the superior vena cava and right atrium may vary considerably since the venous blood from various sources has not yet been well mixed. For example a sample taken near the coronary sinus may have an oxygen content as low as 3 or 4 volumes per cent. Mixing is more complete in the right ventricle and pulmonary artery where the oxygen content usually measures between 10 and 14 volumes per cent.

Under abnormal conditions with congenital septal defects and patent ductus arteriosus there are increased blood oxygen contents in the right atrium right ventricle and pulmonary artery according to the position of the left right shunt pulmonary vascular involvement and certain heart conditions may elevate the pressure readings even to levels as high as three or four times the normal.

### TESTS INVOLVING THE USE OF RADIOACTIVE ISOTOPES

Cutting across various special fields of internal medicine and applicable to a variety of tests in such fields has been the introduction of radioactive isotopes in the years that have followed World War II. Even in therapy also this newly acquired knowledge has played a role, particularly in the form of irradiated iodine to reduce the activity of the abnormal thyroid gland in thyrotoxicosis or of the normal thyroid in combating intractable anorexia pectoris or congestive failure (a medical thyroidectomy). But radioactive isotopes have played a role much more prominently in diagnosis and research than in therapy in cardiovascular disease. In 1942 Hubbard et al used radioactive sodium to determine the velocity of blood flow in infants and young children. This has been followed up since by Prinzmetal et al (1949) who have applied the method to adults. In 1945 Nylin reported the determination of the circulating blood volume by the application of the new method worked out by Hevesy wherein blood corpuscles were tagged with radioactive phosphorus and the time of equilibrium of their dilution curves established by the use of the Geiger counter. In normal cases the circulating blood corpuscles averaged 33.4 gm per kilogram of body weight while in heart failure there was a considerable increase with return to normal figures when the failure cleared. In one case there was a drop of 28 per cent when congestion disappeared. Using the same technic Nylin (1947 1948) has

studied the corpuscular and total blood volume in various organs including the lungs and the heart he found for example that 17 per cent of the total circulating blood volume was to be found in one lung and 13.6 per cent in the lower limbs. Dow et al (1946) and Gibson et al (1946) used radioactive isotopes of iron similarly to measure the circulating red cell volume. Prinzmetal et al (1947) studied the collateral circulation of the normal human heart by coronary perfusion with radioactive erythrocytes and glass spheres and later (1949) used a specially constructed ink-writing Geiger-Mueller counter to record the passage of radioactive blood through the heart chambers which they called radiocardiography. Burch et al (1947) have used radioactive sodium to study congestive heart failure and Smith and Qumby (1947), Elkin et al (1948) and Wright et al (1948) have used radioactive sodium to study the peripheral circulation.

### EXAMINATION OF THE BLOOD

Blood examination affords a wealth of data concerning its various constituents and properties which are sometimes of much value in the study of a patient with cardiovascular disease.

**Hemoglobin.** Usually the hemoglobin in cardiac patients is within normal limits: 80 to 90 per cent by various methods (13 to 15 gm per 100 cc of blood). Slight anemia down to 70 or even 60 per cent hemoglobin may occur in severe or long-continued acute rheumatic heart disease. Moderate to severe anemia down to 55 or even 40 per cent hemoglobin is sometimes present in subacute bacterial endocarditis although slighter grades are more common. The discovery of a low hemoglobin content due to hypochromic anemia of noncardiac origin or to primary pernicious anemia may prove helpful in explaining not only systolic but also diastolic heart murmurs due to cardiac dilatation resulting from the anemia. Sometimes the differential diagnosis between anemia secondary to bacterial endocarditis and that secondary to other factors is difficult. An abnormally high hemoglobin content over 100 per cent is found with polycythemia resulting from congenital heart defects which are attended by cyanosis and a right to left shunt of blood. This percentage of hemoglobin may be as high as 150 (22 gm) or more. Polycythemia vera may in turn be itself a factor of circulatory strain (see Chapter 23).

Recently an iron pigment in muscle called myoglobin which like hemoglobin has a function of picking up and storing oxygen has been under investigation (Björck 1948) but further study is needed to ascertain the clinical significance of variations of its amount in heart muscle.

**Red blood cells.** The red blood corpuscles are decreased below the normal in number relatively less than is the hemoglobin in the anemia of acute rheumatic heart disease and in that of subacute bacterial endocarditis as in almost any secondary anemia. They usually vary between 3 000 000 and 4 000 000 per cubic millimeter according to the severity of the anemia rarely falling to 2 500 000 or 2 000 000 or below in the severest grades of anemia found in



**bacterial endocarditis** In contrast in the morbus caeruleus of congenital heart disease the red cell count is as high as 6 000 000 to 12 000 000

**White blood cells** In infections of the heart the white blood corpuscle counts are increased A slight leukocytosis with a total count of 10 000 to 15 000 per cubic millimeter and a polymorphonuclear percentage of 70 to 85 is common in acute endocarditis rheumatic or otherwise although frequently in mild cases the number of white blood corpuscles is normal in the more severe and fulminating cases of bacterial endocarditis with complications such as embolic infarcts it can be much greater even to a total white count of 30 000 with 95 per cent polymorphonuclear cells Cardiac infarction from coronary thrombosis or embolism usually results in polymorphonuclear leukocytosis for a few days from a slight degree (12 000 with 75 per cent polymorphonuclear cells) to a high degree (25 000 with 90 per cent polymorphonuclear cells) depending on the size of the infarct A small infarct may result in no obvious leukocytosis

**Sedimentation rate** The rate at which the sediment of nonclotted blood settles out is much increased in many disease conditions including the infections involving the heart (rheumatism bacterial endocarditis and tuberculous pericarditis for example) and myocardial infarction from coronary thrombosis It is a useful test not in differential diagnosis but in helping to determine when an active process has completely subsided particularly subacute rheumatism infectious activity in a constrictive pericarditis and active tissue replacement in myocardial infarction It is important to correct the sedimentation rate index for marked variations in the cell volume percentage (hematocrit) of the blood for example a fast rate of 0.5 mm per minute (in a 100 mm sedimentation tube with heparinized blood) in a case with severe anemia may be corrected to a normal rate of 0.25 mm per minute found when the hematocrit is normal (at 45 per cent) (Rourke and Ernste 1930)

**Blood culture** Bacteriologic examination of the blood is occasionally helpful in endocarditis The smear shows no organism but a culture when enough blood 5 to 20 cc is taken and the culture medium hormone broth with a hydrogen ion concentration of pH 7.6 is carefully prepared should reveal the presence of the *Streptococcus viridans* in the great majority of cases of subacute bacterial endocarditis Sometimes several cultures must be taken before positive ones are secured At least three or four positive cultures are essential for complete confirmation of the diagnosis of subacute bacterial endocarditis one or even two positive cultures may be more or less accidental findings Cultures are also useful in determining the particular organism streptococcus staphylococcus pneumococcus gonococcus or rarer bacteria responsible for acute bacterial endocarditis Infrequently in rheumatic endocarditis streptococci have been found in blood cultures and sometimes are thought to be responsible for the infection but blood cultures positive for streptococci have similarly been found in various other diseases and even in relatively normal controls especially when there are chronic foci of infection particularly dental and immediately after tooth extraction (not particularly

after tonsillectomy) This finding is best interpreted as indicating that occasionally stray bacteria may invade the blood stream without causing disease except in rare hearts where there may be suitable soil for their growth as in the case of subacute bacterial endocarditis

**Serologic reactions** Although on rare occasions such serologic tests as those for the gonococcus or the echinococcus may be helpful if carefully carried out it is only the Wassermann or allied (Kahn or Hinton) reaction for syphilis that is of routine value Because of the relative infrequency of cardiovascular syphilis in certain communities this reaction will prove negative in most cardiovascular patients in those communities but in other parts of the world where syphilis is rife and its treatment inadequate a positive Wassermann reaction will be commonly found When it is positive the test is of help in confirming a diagnosis of cardiovascular syphilis made on other grounds or in calling attention to its presence When negative this test for syphilis is of only limited value although the great majority of all patients with cardiovascular syphilis (about 85 per cent) yield positive Wassermann or Kahn or Hinton reactions Even when positive the reaction may be misleading for nonsyphilitic heart disease and incidental syphilis may be present in the same patient also other conditions like jaundice and subacute bacterial endocarditis may rarely yield slightly positive reactions These facts must be remembered and great care and judgment exercised before a positive Wassermann reaction is allowed to influence diagnosis prognosis and treatment there may be a justifiable suspicion of cardiovascular syphilis but symptoms or signs are essential to establish the diagnosis

**Viscosity of the blood** Viscosity of the blood chiefly dependent on its cellular content is rarely an important factor so far as the circulation is concerned and its measurement is largely a matter of academic interest Occasionally however its increase as in high grade polycythemia where it may be as much as three times the normal is a distinct burden for the circulation and a threat for thrombosis it has to be offset in part by capillary dilatation Decreased viscosity occurs in anemia and temporarily in congestive failure or with forcing of fluid intake

**Chemical analyses** Certain chemical analyses of the blood have become of routine value in internal medicine including cardiovascular disease An excess of nonprotein nitrogen beyond the normal upper limit of 40 mg per 100 cc of blood or of urea nitrogen beyond 20 mg per 100 cc means nitrogen retention which in turn means renal insufficiency but usually not primarily renal disease in cardiac patients congestion from heart failure may be the cause An abnormal increase is an accompaniment also of uremia which may be due to poison the heart and of a renal shut-down due to dehydration The amount of blood sugar normally not over 120 mg per 100 cc of blood is worth knowing when diabetes mellitus is suspected because of the frequent association of this disease with early arteriosclerosis and because of its unfavorable effect on heart disease but too low a blood sugar (as from excess of insulin) may also act harmfully in acute coronary heart disease

The serum content of albumin and globulin in relation to cardiovascular disease has not been shown to be of clinical importance in the differentiation of cardiac edema from the edema due to liver disease or to malnutrition. Any one of these factors may complicate the others. In heart failure the serum protein is usually normal in the other two conditions much lowered (to 5.0 gm per 100 cc or less) especially in its albumin fraction. Although it is possible to measure the contents of various ions in the serum (e.g., sodium—normally 136–145 meq per liter potassium—3.5–5.0 meq per liter calcium—9.0–10.5 mg per 100 cc and chloride—100–106 meq per liter), much still remains to be learned about the significance of the blood content of salts and their elements acid and base along with the hydrogen ion concentration which remains strikingly constant (7.35 to 7.45) through buffer action. Suggestions of the significant effect that may result from abnormality of such relationships is shown however in an unusual elevation of the *T* waves of the electrocardiogram in acidosis and in the case of a high potassium content (which may also induce or favor the occurrence of heart block—Thomson, 1939) and depression of the *T* waves in alkalosis and low blood potassium as well as in the case of hypocalcemia (in tetany) in which with very low blood calcium (4 to 5 mg per 100 cc of blood) the duration of systole as measured electrocardiographically is prolonged appreciably beyond the normal dropping again within normal limits when the blood calcium is restored to normal (10 mg). It is also important to remember that the serum content of salts does not indicate the intracellular chemical status. Finally there are other substances for which on occasion the blood should be analyzed e.g. cholesterol in coronary heart disease and thyroid diseases especially (normally 150 to 250 mg per 100 cc serum) and vitamins in suspected avitaminosis (A normally 40 to 100 units per 100 cc C normally 0.4 to 1.0 mg per 100 cc).

**Oxygen in the blood.** The normal content of oxygen in arterial and venous heart blood measured in terms of percentage saturation (if all the hemoglobin were oxygenated the saturation would be 100 per cent) is 95 per cent saturation (18–21 volumes per cent) for arterial blood and about 70 per cent saturation (10–16 volumes per cent) for venous heart blood. For certain parts of the body the venous blood will show a greater degree of unsaturation but this excess is neutralized in the venous heart blood by a lesser degree of unsaturation in other parts of the body. Stasis of varying degree and increased tissue metabolism account for the differences. The more active the metabolism and the greater the stasis anywhere the less oxygen remains in the blood and the bluer it becomes. The dissociation of oxyhemoglobin however requires a favorable temperature and if the air is very cold so that the skin is chilled the peripheral skin circulation although greatly slowed gives not a blue but a red color due to the presence of unreduced oxyhemoglobin.

A helpful instrumental device called the oximeter (Millikan 1932) for the photoelectric determination of blood oxygen saturation in man by standardization against known blood samples can be applied to the ear or even to whole blood via cardiac catheter.

A decrease in amount of oxygen saturation of arterial blood can be of degree it has been found to be as low as 58 per cent in a case of our of congenital heart disease with the tetralogy of Fallot and marked cyanosis (Talbot et al 1941) 32 per cent in a cyanotic and fatal case of the influenza epidemic of 1918-1919 (Stadie 1919) and even per cent in a case of bronchopneumonia with increase to 79 per cent through oxygen inhalation (Meakins and Davies 1925) A decrease in oxygen saturation of arterial blood is due to any one of eight factors as listed herewith (1) Pulmonary congestion from heart (left ventricular) failure may be so great that in the distended pulmonary capillaries much venous blood passes through without contact with the alveolar wall and the oxygen on the other side of that wall also moisture in the alveoli may prevent the proper entrance of air (2) Pulmonary vascular engorgement from mitral stenosis without real heart failure acts in the same way (3) Pneumonic or other consolidation which causes a shunt of venous blood to the left heart through the capillaries of solid lung into which little or no air and oxygen can penetrate may also reduce the oxygen content of arterial blood (4) Destruction of a large amount over half of the total lung tissue may prevent sufficient air from reaching the pulmonary circulation (5) Chronic emphysema and asthma in which the respiratory exchange is very limited may also prevent sufficient oxygen from reaching the alveoli and blood stream (6) High altitudes 10 000 ft (about 3 000 meters) and over where the oxygen content of the inspired air is low do not allow a completely normal oxygen saturation of the blood At 14 200 ft elevation the oxygen saturation of the arterial blood has been found to vary between 80 and 90 per cent instead of the normal of 95 per cent or slightly more (Barcroft and associates 1922) and at 17 500 ft the variation was from 67.6 to 84.6 per cent (average 75 per cent) in six resident healthy workmen (Talbot and Dill 1936) (7) Poisoning by carbon monoxide or other toxic agent to cause methemoglobinemia may prevent some of the hemoglobin from taking up oxygen in the lung (8) Congenital heart disease may be attended by shunts that allow through atrial or ventricular septal defects large enough to allow a considerable amount of venous blood to cross directly into the arterial circulation without first going through the lungs Congenital transposition of the aorta and pulmonary artery may also be a cause

Three additional observations about blood oxygen are of interest In anemia where the hemoglobin is low in amount its saturation with oxygen may be normal and yet the total amount available for the tissues too little With polycythemia as in congenital heart disease the saturation with oxygen may be abnormally low and yet the total content—volumes per cent—be sufficient because of the increased number of red corpuscles Also some oxygen can be carried directly in the blood plasma without attachment to hemoglobin this is not a large amount but it is of some importance the ratio of oxygen so carried to that combined with hemoglobin being about 1 to 50

An increase of oxygen saturation of normal arterial blood can be but slight since it already averages about 95 per cent saturated but when there is oxygen

unsaturation inhalation of air rich in oxygen (for example 50 per cent) may restore the blood saturation to normal

*A decrease of oxygen saturation of venous blood* below the normal arises first from the various factors already enumerated for decrease of oxygen in the arterial blood. The tissues in removing their quota lower the percentage still more sometimes to a level close to zero in marked stasis. Two important factors are added by the peripheral circulation itself (1) increased tissue metabolism from activity and (2) stasis of the circulation. These may simply be local phenomena but if they involve enough of the body a very appreciable decrease of oxygen saturation of the venous blood in the right heart will result.

*An increase of oxygen saturation of venous blood* in the heart above the normal may be found (even up to 94 per cent) when there is a congenital left to right shunt from left atrium to right atrium or from left ventricle to right ventricle or from aorta to pulmonary artery (via patent ductus arteriosus) as determined by cardiac catheterization or when the circulation rate is very rapid and the metabolic activity of the tissues slight as in paroxysmal tachycardia or it may be found locally when there is rapid circulation which does not give time for the usual oxyhemoglobin dissociation or when there is an arteriovenous aneurysm (anastomosis).

**Carbon dioxide in the blood** The carbon dioxide content of arterial blood is normally about 60 volumes per cent i.e. 60 cc of CO<sub>2</sub> gas per 100 cc of blood (26-28 meq per liter milliequivalents per liter = volumes per cent divided by 2.2). The carbon dioxide is carried in the blood chiefly in the form of the dissociated acid sodium salt whereby the carbon dioxide is quickly taken up and given off. If an excess of other acids appears in the blood stream as sometimes happens in diabetes or nephritis the carbonic acid radical is decreased by the blowing off of more than the normal amount of carbon dioxide in the lungs to maintain the normal blood and body reaction. Or there may be a retention of alkali from the blood to neutralize acid in the body tissue with corresponding decrease in the carbon dioxide content of the blood. In alkalosis the carbon dioxide content of the blood is increased.

A decrease, increase or normal amount of carbon dioxide may be found in the arterial blood along with an abnormally low oxygen saturation of this arterial blood though at first thought only an increase might be expected. This variability of carbon dioxide content is dependent on the relative influence of three factors (1) reaction of the blood whether acidotic when in heart failure there is a retention of bicarbonate in the tissues producing a lowered blood carbon dioxide value or alkalotic due to excessive vomiting with elimination of acid gastric juice or to excessive intake of alkalis causing an increased carbon dioxide content in the blood (2) pulmonary overventilation due to oxygen want resulting in a decrease of arterial blood carbon dioxide doubtless a factor in keeping this content low in heart disease and pulmonary underventilation of extreme degree as in very extensive pulmonary disease resulting in excess of arterial blood CO<sub>2</sub> and (3) a shunt of venous blood into the systemic circulation as in marked congenital heart disease.

sufficient to transmit blood with a high  $\text{CO}_2$  content. The product of all these factors determines the carbon dioxide content of the arterial blood. There may be a rise of arterial  $\text{CO}_2$  to as high a content as 85 volumes per cent (in a case of extremely marked pulmonary disease—emphysema and purulent bronchiolitis of the left lung with right lung collapsed by hydrothorax—Meakins and Davies 1925). It may fall to as low as 30 volumes per cent or less from diabetic or uremic acidosis or even from the effect of high altitude (27 volumes per cent in a subject at 14 500 ft elevation—Barcroft and associates 1922) the normal content averaging about 50 volumes per cent. In heart disease with congestive failure and decreased oxygen content of the arterial blood the carbon dioxide content of the arterial blood is more often decreased than normal or increased. The test of alveolar air carbon dioxide has long been used in estimating the degree of acidosis in disease but it is not reliable in certain pulmonary conditions as for example when edema of the lungs is present.

A decrease, increase, or normal amount of carbon dioxide in the venous blood may be found as in the arterial blood but there are two additional variable factors (1) speed of blood flow from arteries to veins and (2) activity of tissue metabolism. If the blood flow is fast or the tissue metabolism decreased less carbon dioxide is delivered to the blood in the capillaries and the difference between the arterial and venous carbon dioxide content may be reduced from a normal average of about 3 volumes per cent to 1.5 or even 1 per cent if the reverse occurs the difference may be increased up to 10 volumes per cent.

Thus in judging the results of blood gas analysis many things have to be taken into consideration including accuracy of technique. The data may prove useful in helping to differentiate congenital heart disease with its shunts from acquired heart disease and in giving actual blood gas measurements for the degree of impairment of the circulation no matter what the cause. The determination of the blood gases directly or by analysis of the alveolar air also permits an estimation of the blood flow that is of the amount of blood pumped by each ventricle per beat and per minute (see page 241).

**Blood volume.** It is of some importance to distinguish between total blood volume in any given person and circulating blood volume they are not synonymous. It has been calculated that the circulating blood volume in an adult of average size equals 5 to 5½ liters that is 3 liters per square meter of body surface or 80 cc per kilogram of body weight (Gordon et al 1935). The mean plasma volume measured by Evans and his associates (1948) amounts to 45 to 50 cc per kilogram of body weight (Cohen et al 1948) the volume of the circulating red blood cells has been determined by use of radioactive phosphorus (Nylon 1945) and iron (Dowling et al 1946) and found to average 30 to 35 gm per kilogram of body weight. Various blood depots will on occasion quite suddenly release a considerable amount of blood from the active circulation to help meet the demand for again by exercise or other requirement. These normal blood depots are the lungs and systemic veins (especially in the splanchnic region).

spleen Abnormal blood depots are most commonly varicose veins of the legs, which may on occasion (chiefly with a change to the standing position) so drain the circulation of blood that faintness or even syncope may occur. Other abnormal blood depots are varicose veins elsewhere than in the legs, lax abdominal vessels and large hemangiomas. These blood depots are overloaded in congestive heart failure and the actively circulating volume of blood is also too great not only for the strength of the heart but in actual amount as well (Gibson 1941) there may be a real hydremia. In vascular shock the circulating volume of blood is on the contrary reduced (see Chapter 30).

Available fluid volumes of the human body can be measured by the dilution of sodium thiocyanate injected intravenously. The subtraction of the plasma volume and 70 per cent of the red cell volume from the total of the available fluid volume gives the available interstitial fluid volume (Morse et al 1947).

### EXAMINATION OF THE URINE

**Quantity** Most important in a patient known or believed to have a failing heart or constrictive pericarditis acute or chronic are the determination and interpretation of the quantity of urine excreted compared to the fluid intake. This should be done not for twenty four hour periods but for twelve hour day and night periods for both fluid output and intake in order to note delay in excretion as well as limitation or excess of flow. These measurements must be made with a reasonable degree of accuracy and fluid excreted by stool also calculated if the bowel movements are watery. We must not forget however that normally a considerable loss of water occurs in the expired air and that the sweat glands of the skin excrete water. Normally there should always be therefore an appreciably larger intake of fluid than output of urine in twenty four hours by a few ounces (100 to 200 cc) at least and by a much larger amount where there is much perspiration. Knowledge of the amount of urine alone is of little value unless this amount is excessively increased or diminished.

If the systemic venous pressure is raised to a high level for a considerable length of time because of congestive heart failure so that fluid which has been distributed to the tissues at the arterial ends of the capillary loops cannot be wholly reabsorbed at the venous ends the output of urine is decreased relative to the fluid intake and also delayed beyond the normal. If the osmotic pressure in the capillaries is much decreased because of low serum protein as in nephrosis and malnutrition fluid leaves the circulation in too large an amount and the urine output decreases. In either case a decreased urinary output is often a good warning of an impending edema. With the beginning of diuresis the amount of urine increases and approaches and often surpasses the fluid intake and edema if present begins to subside. It is well to keep a chart of these two measurements routinely day and night in the case of a cardiac patient with congestive failure of any grade at all.

**Specific gravity** The specific gravity of the urine is of less moment than the quantity but usually varies with it. When the urine output is much decreased in congestive heart failure the specific gravity tends to be high due to concentration (1.025 to 1.030) but in spite of a slight to moderate albuminuria it is not so high as with a like degree of oliguria in health when the function of normal uncongested kidneys permits full concentration (1.030 to 1.040 or more). When there is a large flow of urine with diuresis the specific gravity usually varies very little and tends to be low under 1.010. If there is poor renal function especially in chronic nephritis the night amount tends to exceed that of the day and the specific gravity usually maintains a fairly constant figure.

The urine concentration test of renal function systematically introduced by Volhard (1918) but simplified by Fishberg (see his fourth edition of *Hypertension and Nephritis*, Lea and Febiger Philadelphia 1939 page 77) is the most practicable of the various functional tests of the kidney for routine use. Briefly it is as follows. On the day and night of the test the subject drinks no fluid after the noon meal eating a dry supper. The urine passed during the afternoon and at bedtime is discarded as well as any during the night. The first urine passed in the morning is saved in a bottle. After an hour more in bed a second specimen is passed into another bottle and still a third after being up and around for an hour without eating or drinking. Fishberg writes

The specific gravity of each of the three specimens is then taken. If kidney function is unimpaired the specific gravity of at least one of the specimens will exceed 1.022 often going as high as 1.032. In very severe impairment of renal function the maximum specific gravity is but 1.010 and in intermediary cases figures between these extremes are obtained. In every case exhibiting low specific gravity it is important to observe if edema is being evacuated for this may simulate inability to concentrate. The third specimen passed while the patient is up and about occasionally helps in the detection of orthostatic albuminuria.

**Albumin** Albuminuria is an almost constant finding in congestive heart failure the greater the congestion the more the albuminuria. In the absence of any trace of edema its presence is far more significant of renal disease unless it is the slight inconstant so called orthostatic albuminuria or an accompaniment of infection. In the case of subacute bacterial (*Streptococcus viridans*) endocarditis there is often important renal bleeding and damage albuminuria is therefore a frequent finding in this disease.

**Sugar** Glycosuria may be transient slight and unimportant it may be of alimentary origin or the result of some accident like cerebral hemorrhage but usually it indicates diabetes mellitus mild or severe and then demands particularly conservative treatment in cardiovascular patients (see Chapter 23).

**Urinary sediment** Generally when there is congestive albuminuria red and white blood corpuscles and granular and cellular casts are found in the sediment of the urine. With chronic nephritis hyaline casts are more frequent than in congestive heart failure. With subacute bacterial endocarditis even though



there be no albuminuria red blood corpuscles are usually found in the sediment Gross blood in the urine is always important but is more likely to be due to local infection stone or malignancy than to heart disease Renal infarction secondary to emboli from a diseased heart in subacute bacterial endocarditis myocardial infarction with intracardiac thrombosis or mitral stenosis with atrial fibrillation is however an occasional cause of gross hematuria

**Renal function tests** The various tests of renal function simple or more elaborate may be applied in the presence of cardiovascular disease but their interpretation must be guarded The disturbance of renal function may be dependent on either renal disease or secondary congestion from heart failure The degree of renal impairment as indicated by most of the functional tests is dependent rather on the degree of involvement of the kidneys whether primary or secondary than on the type of involvement The combination of both primary and secondary involvement naturally results in the gravest disturbances of function One must wait until congestive failure subsides before making many deductions from renal function tests The most practical and useful tests are the urine concentration test such as that described above under Specific Gravity and the red (phenolsulfonphthalein) test in current use everywhere emphasizing however more the rapidity than the amount of the excretion it is more important to know what percentage of the dye is excreted in the first 15 minutes (normally 25 per cent or more) than in the total time of two hours (60 per cent or more)

### CARDIAC OUTPUT MINUTE VOLUME OF BLOOD FLOW AND CIRCULATION RATE STUDIES PLETHYSMOGRAPHY

**Cardiac output** The cardiac output the minute volume of the blood flow and the speed of the circulation have been subjects for physiologic investigation for years chiefly in animals in the experimental laboratory During the last decade the application of such study to clinical medicine has been successfully begun

Long ago it was shown experimentally that the amount of blood pumped out by either ventricle in the course of a minute called the *minute volume of blood flow* could be determined readily by a formula (Fick 1870) based on the amount of oxygen taken up by the lungs in a minute's time and the amount utilized by the tissues This formula is as follows

$$\text{Minute volume of blood flow} = \frac{100 \times \text{cubic centimeters oxygen consumed in lungs per minute}}{\text{Difference in volumes per cent between oxygen content of arterial blood and that of venous blood}}$$

(in cubic centimeters)

The application of this formula to man was for years fraught with difficulties though the discovery that analysis of the alveolar air permitted a close ap-

proximation to that of the blood gases of the right and left sides of the heart proved very helpful so that the minute volume of man could be ascertained and through that the stroke volume or output of each ventricle per beat (by dividing the minute volume by the pulse rate) Another method for determining blood flow was also used dependent on the absorption of certain gases from the lungs in a certain unit of time for example nitrous oxide acetylene and ethyl iodide acetylene proved to be the most suitable gas for this study (Grollman 1932) ethyl iodide giving figures 33 per cent too small

The introduction in recent years of cardiac catheterization has permitted a more accurate determination of the minute volume of blood flow by the use of the Fick formula since the oxygen content of the mixed venous blood in the right heart chambers can be readily measured and compared with the oxygen content of arterial blood This volume divided by the pulse rate gives the cardiac output per beat

Hamilton and his associates (1947 and 1948) have compared the Fick dye injection and pressure pulse curves in dog and man in relation to the cardiac stroke volume and have found a fair correlation between the dye injection and Fick findings and a close approximation between dye injection and pulse pressure contour

The application of heart volume changes between systole and diastole as determined roentgenologically has also been suggested recently (Hubacher and Nyfleler 1946) the difference in volume representing directly the stroke volume The difficulties inherent in measuring the heart volume by x ray however present a problem here that needs further development (see Chapter 7)

An ingenious but crude method of determining the output of the heart per beat and per minute was introduced by the use of the *ballistocardiograph* (Starr and Schroeder 1940 Cournaud Ranges and Riley 1942) This instrument which consists of a delicately balanced table (on which the subject reclines) records the recoil of the body when the blood is ejected into the aorta and pulmonary artery from the ventricles Attempts have been made to correlate the graphic record which results called the ballistocardiogram (see Chapter 8) with the output of the heart as determined by the more direct methods noted above and can apparently with considerable corrections be used as a rough though inadequate gauge of the cardiac output the latest studies have indicated that the ballistocardiographic index was about one third too low Thus ballistocardiography is best used as a method of study per se and not to determine the cardiac output (see Chapter 8 and Figure 38 page 172)

The minute output at rest normally ranges from 3 500 to 9 000 cc (6 to 12 cc per 100 gm of body weight) being increased by exercise to as high as 25 liters or more in some cases It may like the stroke volume be reduced by various factors but usually to a less degree since an increase of pulse rate tends to compensate for a decreased output per beat The erect posture has been found usually to cause a decrease (even as much as 30 per cent or more

but usually less) of the minute volume calculated for the recumbent position. Various other factors influence blood flow in a definite but sometimes indeterminate degree: these are the stroke volume of the heart, the lung capacity, the absorption power of the lungs, and the capillary diffusion areas of muscles. Physical training makes these factors more favorable and so enables the circulation to be carried on more economically with less strain on heart and arteries, as indicated by less elevation of pulse rate and blood pressure on exertion in the athlete than in the nonathlete. Heart failure is usually attended by a decreased output, but this is very variable and in some cases, as in thyrotoxicosis, the output may still be elevated.

It has been found that the normal output per beat or stroke volume varies in the average adult from 50 to 100 cc at rest but that in athletes it may be much higher, even 150 cc or more. This is increased by exercise, less in the nonathlete than in the athlete; it may be more than doubled, rising for example from 60 to 130 cc or from 70 to 150 cc on vigorous exercise. With heart failure or extreme tachycardia it may be reduced; in a case of paroxysmal tachycardia, for example, it has been reported to have dropped from 77 to 13 cc (Barcroft, Bock, and Roughton, 1921).

**Circulation rate.** In the past the volume of blood flow has been studied more than the rate, but ingenious methods for determining the rate of blood flow through important parts of the circulatory system have been devised. A pioneer method consisted of the injection of an active deposit of radium into the vein of one arm and the determination by means of a detector of the moment of its arrival in the heart and in the artery of the other arm (Blumgart and Yens, 1927; Blumgart and Weiss, 1927). The speed of flow from arm vein to heart and through heart and lungs to arm artery was thereby roughly determined. Normally this arm to arm circulation time was found to vary from 14 to 24 seconds (average 18 seconds), a somewhat longer time than has been the finding in the case of more recently introduced substances injected; this time increased with the pulse rate but not with blood pressure variations and was not affected by valvular disease. The circulation rate was found to be decreased in congestive heart failure according to the degree of failure, and also in atrial fibrillation without failure. Arteriosclerosis and pulmonary emphysema did not cause a delay. The arm vein to heart rate of travel of the radium injected blood showed a wide range of 2 to 14 seconds with an average of 7 seconds in normal individuals.

The recent introduction of the employment of safe radioactive isotopes has revived this earliest method of determining the circulatory rate. Hubbard et al. (1942) tested the velocity of blood flow in infants and young children using radioactive sodium. Prinzmetal et al. (1949) found the arm to right heart time to average 2 seconds normally in the adult with an additional 5 or 6 seconds to the left heart.

Since the earlier days of the clinical application of the study of the rate of the circulation a decade or more ago, numerous new methods, consisting mostly of substances for injection into an arm vein, have been introduced.

These have included injections of a dye (brilliant vital red for example) fluorescein histamine (which flushes the face) sodium cyanide (causing a sharp increase in respiration) lobeline (causing a deep inspiration followed by a cough) Decholin (sodium dehydrocholate) (giving a bitter taste) glucose or saccharine (detected in the systemic circulation of the tongue by a characteristic taste) aminophyllin amyl nitrite (lung to face time as determined by a hot sensation) and calcium gluconate and magnesium sulfate (both causing a sensation of heat in pharynx and tongue) to test the rate of the blood flow from the venous side of the systemic circulation through the right heart lungs and left heart into the arterial side of the systemic circulation. There is a wide range of sharpness of end point and of practicability among these various substances. Hitzig (1947) and Blumgart and Altschule (personal communication) have preferred the use of Decholin with end point at 10 to 16 seconds which however has in rare cases caused allergic like reactions (Norman 1947). Baer (1940) found calcium gluconate the most desirable in 133 normal persons he found the arm vein to tongue time to range from 8 to 16.5 seconds averaging 12.3 seconds. He injected 4 cc of 20 per cent calcium gluconate rapidly and then again in 2 or 3 minutes. Papaverine HCl has also been suggested for determining the circulatory rate (Elek and Solarz 1942) 40 mg (1.25 cc) being the dose recommended an average of 20.8 seconds (15.4 to 27.0) has been reported between the time of injection and that of the end point a sudden deep inspiration. In experimental animals acetylcholine has been tried with end point measured by direct inhibitory effect on sinoatrial node (Wilburne et al 1947).

To test the arm to lung time that is the integrity of the venous side of the systemic circulation and the right heart the injection of ether (Hitzig 1935) has been most practicable (using 5 minims of ether and 5 minims of normal saline) with end point detected by the subject's consciousness (or even the observer's note) of the presence of ether on the breath. Baer (1940) found the ether arm to lung time in 169 normal individuals to vary from 3 to 9 seconds averaging 5.3 seconds. Paraldehyde has also been introduced to test the arm to lung time (Caudel 1938)—the end point is shown by a cough in 100 adults with normal hearts the range was from 3 to 9.5 seconds averaging 6 seconds.

Finally the inhalation of CO has been suggested to test the lung to brain time that is the integrity of the pulmonary circulation and left heart (Gubner Schnur and Crawford 1939) acting as a stimulant to the respiratory center its normal range has been found to be 5 to 10 seconds.

Several investigators (Germandt and Nylin 1946 Mencely and Chestnut 1947 Nathanson and Elek 1947) have pointed out the delay in circulation rate that may occur as the result of dilatation of the heart alone even without congestive failure there remaining a certain amount of residual blood in the heart chambers immediately after their contraction.

The tests of circulatory rate ordinarily employed are the ether time (normal average about 6 seconds) to determine the state of the right ventricle and

Decholin saccharine, or cyanide time (normal average 12 to 15 seconds) to test the total heart efficiency the subtraction of the former from the latter gives an estimate of the strength or failure of the left ventricle. The tests are useful in a few cases in which there is some doubt especially in distinguishing obscure cases between bronchial and cardiac asthma and in following given patients by serial tests but they are not routinely necessary.

**Plethysmography** : Plethysmography that is the measurement of volume changes of extremity or organ has been carried out chiefly in experimental animals but for certain purposes has been also applied to man. It has been used to measure blood pressure to obtain fairly accurate records of the arterial pulse wave and especially to measure the volume of blood flow in a special part of the body. It has little application to routine cardiovascular examination but in obscure or difficult cases of peripheral vascular disease it may yield information of value. Of late a study of the electrical impedance of an extremity has indicated its possible use in the application of an electrically recording plethysmograph to investigations of the peripheral circulation (Nyboer 1950).

#### CALCULATION OF THE WORK OF THE HEART AND OF THE PULSE

Various attempts have been made to estimate the actual work of the heart and of the pulse some of these have proved of interest but they have not been of any practical value in cardiovascular examination. We can for example express by a very rough formula the work of the left ventricle when we know the volume output per beat the heart rate and the mean arterial blood pressure. If the left ventricle expels 100 cc of blood per beat at a rate of 60 beats per minute at a mean arterial pressure of 100 mm of mercury (about 1 300 mm of blood) it lifts 6 liters (6 000 cc) of blood to a height of 10 cm of mercury (or about 130 cm of its own weight) per minute which equals 780 000 gm-cm (or 7.8 kg meters) per minute. The blood vessels maintain this volume at a somewhat lower level through diastole in addition to withstanding the systolic shock of the heart. This rough calculation expresses in an interesting way the enormous constant activity of the heart. It may further be applied to certain pathologic states for example if the mean arterial blood pressure is 150 mm of mercury and the heart rate 60 per minute and the output per beat 100 cc the work of the heart is 50 per cent greater than in the previous example given or 11.7 kg meters per minute. Such a great increase in work if constant can explain the hypertrophy of the left ventricle found in hypertension.

It has been calculated (Remington and Hamilton 1947) that the cardiac work performed in maintaining pressure is underestimated up to 12 per cent by multiplying the total ejection by the mean pressure during systole and that the work done by the heart in raising the pressure of the blood is 10 to 40 per cent more than that done at the periphery in forcing blood through the peripheral resistance energy to this amount being lost as the aortic wave is damped.

More accurate formulas to include still other variables like velocity the effect of gravity and time intervals have been devised such as the following (Evans 1918)

$$\text{Work of heart} = 7 \frac{Q \times R}{6} + \frac{W (V \times C)}{G \times E} \quad \text{where } Q \text{ equals the quantity of}$$

blood ejected  $R$  equals the mean arterial resistance in meters of blood  $W$  equals the weight of the volume ejected  $V$  equals the mean velocity  $C$  equals the duration of the cardiac cycle  $G$  equals the acceleration due to gravity and  $E$  equals the period of systolic ejection. The complication and incompleteness of such a formula however renders it impracticable except for experimental animals moreover it represents not the work of the whole heart but of the left ventricle alone. The need of determining the output of the heart per beat by special methods the difficulty of ascertaining the mean arterial pressure the need of cardiac catheterization to estimate accurately the work of the right ventricle because for such calculation the pulmonary blood pressure must be measured in man and the apparent relative unimportance of the knowledge of the exact amount of work done by the heart have caused the general and probably justifiable neglect of such calculations as these in cardiovascular examination. It is possible however that more attention paid to the actual work of the heart would be helpful at least in causing one to realize the great variability that exists not only in disease but also in health.

Calculation of the work of the pulse as determined for example by sphygmobolometry (Sahli) or ergometry (Christen) or otherwise has proved very complicated and of no practical value.

## FUNCTIONAL TESTS OF THE HEART AND OF THE CIRCULATION

**Strength and endurance tests** Both simple and complicated measures of strength and endurance have been proposed to gauge the health of the heart muscles and of the circulation as a whole. These measures do demonstrate efficiency of the heart along with that of the muscles and nerves but it is frequently difficult to conclude to what degree abnormal limitation of strength and endurance is due to exhaustion how much to nervous fatigue and how much to myocardial weakness. Dyspnea and angina pectoris are the two chief cardiac symptoms of overtaxation of the myocardium and when these symptoms are clearly singly and in a preponderant degree produced by tests of physical activity we may obtain valuable information about the heart. When a sense of exhaustion in local muscles or generally throughout the body or when palpitation dizziness and faintness appear with or without dyspnea or heartache (not angina pectoris) other factors then enter in which prevent carrying the exertion far enough clearly to test the heart's strength this is the usual situation because of the general lack of physical training or because of the ready nervous fatigability in most individuals tested. Hence these tests of strength and endurance generally amount to tests of training and of the nervous

state that is of physical fitness rather than of cardiac condition Neurocirculatory asthenia (or effort syndrome or soldier's heart) and muscular flabbiness are more easily and often exposed by exercise tests than is heart disease Nevertheless tests of strength and endurance may be applied with some success in estimating myocardial efficiency if sound judgment be shown in the interpretation of the findings

The simpler the test the better because a simple test is less likely to strain unaccustomed muscles less likely to exhaust prematurely is a person not in good physical training and more convenient and practical to execute In fact such simple exertion as enters into the routine daily life of the patient is best of all Questioning alone may suffice as to the production of dyspnea or of angina pectoris by climbing a flight or two of stairs at an ordinary rate of speed climbing a hill of moderate grade at moderate pace walking fairly rapidly on the level or lifting and carrying a handbag suitcase or heavy overcoat But if there is doubt or a need for exact data actual tests of these activities under the observation of the examiner should be executed Climbing a flight or two of stairs or if that seems too much pacing rapidly up and down the room or corridor or mounting and descending repeatedly an especially constructed two-step footstool are perhaps the best of the simple exercise tests A word of warning should however be added here namely that exercise testing in the case of serious coronary insufficiency can prove fatal

Under some circumstances as for example in examinations for military service athletic sport or other such activities more vigorous or special tests are suitable such as weight lifting hopping running and stepping repeatedly from floor to chair seat and back again Since however in routine civilian practice one deals often with older men and women or untrained persons with weak or undeveloped muscles these exercises are not usually applicable A trained athlete physically fit but with well marked aortic regurgitation may carry out vigorous exercise tests without any trouble while an untrained soft muscled man of the same age height and weight with a normal heart may be unable to complete relatively light exercise tests without much fatigue dyspnea and palpitation

The reaction of pulse rate and of blood pressure to exercise has been the subject of considerable study and discussion and has at times been thought to be a suitable test of circulatory efficiency, but the same remarks apply to this as to the production of symptoms Too marked a rise of pulse or blood pressure and too long a duration of this rise after rest begins go with poor physical condition as often as with cardiac weakness alone Normally after a short spell of exercise of moderate degree (like climbing rapidly two average flights of stairs or lifting during a time interval of one minute two five-pound dumbbells twenty times from the floor first to a standing position and then to an extended position of the arms above the head) the pulse rate and blood pressure in a well trained young or middle aged adult should return to normal from elevated levels within two minutes after lying down The more vigorous the exercise the more slowly do blood pressure and pulse rate return

to resting figures even in the normal subject. The delayed rise of pressure is also of little or no significance normally there is a slight immediate fall when exercise begins before the rise develops.

Over a period of many years various functional tests have been introduced under the names of their respective proposers but thereafter as a rule speedily forgotten. Cabot and Bruce for example in 1907 described a group of such tests and imposed a modification of their own. There has however been in routine use for quite some years especially in military circles a certain test for general physical and circulatory efficiency which despite its obvious imperfections has continued to be commonly employed. This is the Schneider Index (1920). It is carried out as follows:

1. The patient reclines for five minutes. (a) The heart rate is then counted for twenty seconds. When two consecutive twenty second counts are the same this is multiplied by 3 and recorded. The score is noted according to Part A Table 1. (b) The systolic blood pressure is next taken by auscultation two or three readings are made as a check.

2. (a) The patient stands at ease for one or two minutes to allow the pulse to assume a uniform rate. When two consecutive twenty second counts are the same this is multiplied by 3 and recorded. The score is obtained by the use of Part C Table 1. The difference between the standing and reclining pulse rate is scored then by use of Part B Table 1. (b) The standing systolic pressure is next taken. The difference between this and the reclining systolic pressure is then scored by Part F Table 1.

3. The patient next steps on a chair about 18 inches high, five times in fifteen seconds timed by a watch. To make this test uniform he stands with one foot on the chair at the count one this foot remains on the chair and is not brought to the floor again until after the count five. At each count he brings the other foot on the chair and at the count down replaces it on the floor. This should be timed accurately so that at the fifteen second mark both feet are on the floor. (a) Immediately while he stands at ease the pulse rate is counted for fifteen seconds this is multiplied by 4 and recorded. (b) Counting is continued in fifteen second intervals for two minutes record being made of the counts at 60, 90 and 120 seconds.

The data from (a) will be scored by Part D Table 1 taking the difference between this exercise pulse rate and the standing rate. The data in (b) are scored according to Part E Table 1.

The total score is then added up in Parts A, B, C, D, E and F of Table 1 (see next page). The maximum possible is plus 18 and the minimum is minus 11. A score above plus 9 is considered normal a score of 9 or less fails to pass and is reason for a search as to the cause.

A newer test of physical fitness for strenuous exertion superior in its application to athletes and simpler in its execution than the Schneider Index was developed at the Harvard Fatigue Laboratory and is called the Fatigue Laboratory Index (Johnson, Brouha and Darling 1942). It is carried out as follows. The subject works at a standard hard exercise until he is exhausted.



or if not exhausted for five minutes. The pulse is counted in recovery from 1 to 1½ from 2 to 2½, and from 4 to 4½ minutes. The score is calculated from the formula

$$\text{Index of fitness for hard work} = \frac{\text{Duration of exhausting work in seconds} \times 100}{2 \times \text{sum of pulses from 1-1}\frac{1}{2} \text{ 2-2}\frac{1}{2} \text{ and 4-4}\frac{1}{2} \text{ minutes after the end of work}}$$

The larger the score the better the subject 100 being a very good score. Any form of exercise can be used provided it puts sufficient stress on the circulatory system by involving large muscle groups provided not more than two

Table 1

POINTS FOR GRADING CARDIOVASCULAR CHANGES IN SCHNEIDER'S TEST OF PHYSICAL FATIGUE AND EFFICIENCY

# SCHNEIDER INDEX

## A Resting pulse rate

Rate	Points
50-60	3
61-70	3
71-80	2
81-90	1
91-100	0
101-110	-1

## B Pulse rate increase on standing (points)

0-10 Beats	11-18	19-26	27-34	35-42
3	3	2	1	0
3	2	1	0	1
3	2	0	-1	2
2	1	-1	-2	-3
1	0	-2	-3	3
0	-1	-3	-3	3

## C Standing pulse rate

Rate	Point
60-70	3
71-80	3
81-90	2
91-100	1
101-110	1
111-120	0
121-130	0
131-140	-1

## D Pulse rate increase immediately after exercise

0-10 Beats	11-20	21-30	31-40	40-50
3	3	2	1	0
3	2	1	0	0
3	2	1	0	1
2	1	0	-1	-
1	0	-1	-2	-3
1	-1	-2	-3	3
0	-2	-3	-3	-3
0	-3	-3	-3	-3

## E Return of pulse rate to (standing) normal after exercise

Second	Points
0-30	3
31-60	2
61-90	1
91-120	0
After 120 two to ten beats above normal	-1
After 10 eleven to thirty beats above normal	-

## F Systolic pressure standing compared with resting

Change in mm.	Points
Rise of 8 or more	3
Rise of 2-7	2
No rise	1
Fall of 2-5	0
Fall of 6 or more	-1

thirds of the subjects can maintain it for five minutes and provided it does not demand some unusual skill for its successful performance. The only equipment needed is a stopwatch and a means of administering a known amount of exercise at a constant rate. Detailed instructions are given for using the test when a treadmill is available.

**Respiratory tests** Most of the respiratory tests that have been employed to study circulatory efficiency are restricted in the same way in their clinical application as are the strength tests described above. But here a further complication exists. Diseases of the lungs, pleurae or respiratory muscles can cause striking reductions in scoring just as can general weakness, neurocirculatory asthenia and certain cardiac lesions.

There are various respiratory tests, the most practicable two being that of the vital capacity and that measuring the length of time that the breath can be held. More complicated tests which measure symptom and pulse and blood pressure reactions to certain respiratory efforts such as maintaining an elevated air pressure in a closed system for a certain length of time or re-breathing air in a closed chamber are open to the same objections as those already expressed concerning exercise tests; they are tests of physical fitness more than of heart disease or failure, also they are affected at times by the additional factor of possible pulmonary disease. Although they may reveal myocardial insufficiency, the degree of this must be very carefully interpreted and judged.

**Vital capacity** The vital capacity of the lungs is the measurement by spirometer of the amount of air in liters that can be expelled by a complete forceful expiration after the fullest possible inspiration. This test was first studied in considerable detail over a century ago (Hutchinson 1846). Normally the vital capacity varies with the size of the individual which is best calculated from the surface area; the surface area can in turn be estimated roughly but accurately enough from the height and weight. The normal ratio averages 2.5 liters of vital capacity per square meter of body surface. A chart has been devised for the determination of surface area (Figure 28B, page 143) and tables of average normal vital capacity for male and female American subjects have been constructed. The vital capacity ranges normally from 3 to 4 liters for adult females and from 4 to 5 liters for adult males. It varies somewhat with practice, increasing as a rule on repeated tests until the subject becomes expert. It varies also with physical fitness. An athlete has a higher vital capacity than a nonathlete by as much as 25 per cent or more. Furthermore, the vital capacity is between 5 and 10 per cent higher in the erect than in the recumbent position. In severely exhausted states and in marked neurocirculatory asthenia it may be much reduced, even to 2 liters or less, in an adult who is otherwise healthy with normal heart and lungs. If inexperience, exhaustion and lack of physical training are excluded as factors, vital capacity reduction means infection, thyrotoxicosis or pulmonary, pleural, mediastinal or cardiac disease.

Vital capacity was originally studied to ascertain the degree of pulmonary

disease such as phthisis in which it is usually reduced. Of primary cardiac conditions there are chiefly two that give rise to reductions of vital capacity: mitral stenosis and congestive heart failure. Pulmonary emphysema, no matter what may produce it fundamentally, is also an occasional cause of reduction of the vital capacity. The greater the degree of any of these conditions, cardiac or otherwise, the lower is the vital capacity, especially in the case of heart failure when there may be a reduction to below a liter. Such a high degree of reduction does not happen with uncomplicated mitral stenosis. It has been reported that if there is pulmonary edema, breathing dry air may increase the vital capacity as much as 10 per cent or more (Leas 1927).

The chief value of the vital capacity measurement in the study of a cardiac patient is in following the course of congestive failure. A chart showing the vital capacity at intervals, daily or every few days, is of interest and sometimes of value in such cases, but the test is a crude one and lags behind other evidence of change in the patient as often as it precedes it. It may be concluded that the estimation of vital capacity in cardiovascular examination is not important as a routine measure, except perhaps in pregnancy with heart disease when exertion is by order much restricted and reduction of the vital capacity may be the first indication of impending heart failure. It is not delicate enough to demonstrate very slight grades of cardiac insufficiency and it does not give evidence of organic heart disease in the absence of failure, except in the case of mitral stenosis which acts to decrease the alveolar air by causing engorgement of the lung vessels.

*Breath holding test.* A very simple respiratory test, probably as useful as any other, and because of its ease of execution the most practicable, is the measurement of the length of time the breath can be held after a full inspiration. All the qualifications with respect to the circulation made above concerning exercise and respiratory tests apply here also. The breath holding test has one defect which applies only to certain cases, and that is the possibility of malingering, noted sometimes in soldiers during World War I; it is possible, however, with experience to detect malingering. Practice is sometimes important, as in the case of the vital capacity test. A normal person in good physical and mental condition should be able to hold the breath for more than half a minute, usually about three quarters of a minute and occasionally for over a full minute. Extensive and expert training in underwater swimming and diving may enable an individual to hold his breath as long as two or three minutes or even a bit longer. If the breath cannot be held as long as a half minute, the test shows abnormality, consisting of pulmonary or pleural disease, congestive heart failure or lesser grade of cardiac insufficiency, mitral stenosis, general weakness, or neurocirculatory asthenia.

*Anoxemia test.* The so-called anoxemia test was clinically introduced by Levy and his associates in 1939 to determine the functional capacity of the coronary circulation, especially in persons suspected of having coronary heart disease but without clear-cut angina pectoris or electrocardiographic abnormalities. The test is carried out as follows: The subject breathes a mixture of

10 per cent oxygen and 90 per cent nitrogen for twenty minutes unless cardiac pain is experienced before the end of that time. Electrocardiograms (preferably the precordial leads first) are taken routinely just before the test is started and at intervals of five minutes thereafter. If the patient complains of discomfort a record is quickly taken, the low oxygen mixture is shut off and 100 per cent oxygen administered for one minute.

Two hundred and ninety three of these tests were carried out by Dr. Levy and his associates. 136 were done on persons apparently free of cardiac diseases and 157 were done on patients with coronary sclerosis. Pain was not induced in any of the normal cases. 74 or 47 per cent of the coronary cases complained of pain in 54 of which the pain came on during the first 10 minutes. Positive electrocardiographic tests were observed in 77 or 49 per cent. Positivity of the test was considered to be a total *RS* *ST* deviation greater than 2.5 mm. Deviation was most marked in Lead I and in the precordial leads.

The test has been found useful by Levy and his associates in doubtful cases but has not yet been widely adopted. Some question of its safety has been raised and of the interpretation of slight electrocardiographic variations which might be within the range of normal (Burnett et al. 1942) but in the hands of Levy and his associates (1941 and 1942) and of others since the test has apparently proved both useful and safe. Careful clinical appraisal however makes rarely necessary either this anoxemia test or exercise tests though there are always a few individuals in whom the diagnosis may be difficult and for whom such tests are helpful if positive. Negative tests do not however rule out serious coronary heart disease with certainty.

**Tests of the peripheral circulation.** Numerous tests of the efficiency of the peripheral circulation have been introduced from time to time. A decade ago a review (Montgomery Naide and Freeman 1941) summarized their diagnostic importance. The tests have been divided into four groups: (A) those which are a part of the physical examination and include observation of local tissue nutrition, color and temperature of skin, palpation of pulse and estimation of blood pressure in different limbs at various levels, rate of blanching on elevation and of flushing and filling of veins on dependency and the reproduction of spasm by immersion of the extremity in cold water; (B) tests of capacity of blood flow (vascular function tests) in skin as shown by vasodilatation by reflex heat, artificial fever, anesthesia (local, general, spinal and paravertebral), intradermal histamine and saline injections and reactive hyperemia; (C) tests of capacity for blood flow (vascular function tests) in muscle by walking certain distances and by ergographic measurements of muscle fatigue; and (D) test of past damage to arteries by oscillometry and roentgen ray studies, especially by Diodrast injection of arteries or veins. An additional method of study (E) has been more recently introduced consisting of the injection of radioactive isotopes, especially sodium, and following its course through any local circulatory area by Geiger counter (Elkin et al. 1948). As in the case of judgment about the heart by tests, so here too much

experience and common sense are needed for proper appraisal in many of the cases

## BIBLIOGRAPHY

### OTHER METHODS OF EXAMINATION

#### Cardiac Catheterization

- Bing R J Vandam L D Gregoire F et al Catheterization of Coronary Sinus and Middle Cardiac Vein in Man *Proc Soc Exper Biol & Med* 1947 LXVI 239
- Bradley ■ ■ Variations in Hepatic Blood Flow in Man During Health and Disease *New England J Med* 1949 CCXL 456
- Burchell H B Parker R L Dry T J et al Cardiac Catheterization in Diagnosis of Various Cardiac Malformations and Diseases *Proc Staff Meet Mayo Clin* 1948 XXIII 481
- Cournand A Baldwin J S and Himmelstein A *Cardiac Catheterization in Congenital Heart Disease* The Commonwealth Fund New York 1949
- Cournand A and Ranges H A Catheterization of the Right Auricle in Man *Proc Soc Exper Biol & Med* 1941 XLVI 462
- Dexter L Venous Catheterization of Heart II Results Interpretations and Value *Radiology* 1947 XLVIII 451
- Forssmann W Die Sondierung des rechten Herzens *Klin Wchnschr* 1929 VIII 2085
- Landtman B "Mechanically Induced Disturbances in the Heart Action Observations Made on Heart Catheterization of One Hundred and Forty two Children *Acta paediatrica* 1950 XXXIX 1
- Lenegre J and Maurice F La pression ventriculaire droite *Paris med* 1945 CXXIX 21
- Limon Lason R Rubio Alvarez V and Bouchard F El cateterismo intracardiaco V Cateterizacion de las cavidades izquierdas en el hombre Registro simultaneo de presion y electrocardiograma intracavitarios *Arch del Inst de cardiol Mexico* 1950 XX 271
- Sosman M C Venous Catheterization of the Heart I Indications Technics and Errors *Radiology* 1947 XLVIII 441
- Soulie P Carlotti J Joly Fr and Scot J R Catheterisme du sinus coronaire (Étude détaillée de 11 cas) *Arch d mal l coeur* 1949 XLII 818
- van den Heuvel Heymans G Procaine amide (pronestyl) et arythmies cardiaques au cours du catheterisme du coeur *Acta cardiol* 1951 VI 53
- Warren J V Stead E A Jr and Brannon E S Cardiac Output in Man Study of Some of Errors in Method of Right Heart Catheterization *Am J Physiol* 1946 CXLV 458
- Zimmerman H A Scott R W and Becker N O Catheterization of the Left Heart in Man *Circulation* 1950 I 357

#### The Use of Radioactive Isotopes

- Burch G Reaser P and Cronvich J Rates of Sodium Turnover in Normal Subjects and in Patients with Congestive Heart Failure *J Lab & Clin Med* 1947 XXXII 1169
- Dow P Hahn P F and Hamilton W F "The Simultaneous Transport of Tl<sup>201</sup> and Radio active Red Cells Through the Heart and Lungs *Am J Physiol* 1946 CXLVII 493
- Filkin D C et al "The Study of Peripheral Vascular Disease with Radioactive Isotopes Part I *Surg Gynec & Obst* 1948 LXXXVII 1
- Gibson J G 2nd et al "The Measurement of the Circulating Red Cell Volume by Means of Two Radioactive Isotopes of Iron *J Clin Investigation* 1946 XXV 616
- Hubbard J P Preston W N and Ross R A "The Velocity of Blood Flow in Infants and Young Children Determined by Radioactive Sodium" *J Clin Investigation* 1942 XXI 613

- Meneely G R Wells E B and Hahn P F Application of Radioactive Red Cell Method for Determination of Blood Volume in Humans *Am J Physiol* 1947 CXLVIII 531
- Nylin G Blood Volume Determinations with Radioactive Phosphorus *Brit Heart J* 1945 VII 81
- Circulatory Blood Volume of Some Organs *Am Heart J* 1947 XXXIV 174
- Nylin G and Hedlund S Further Studies of the Circulation with Radioactive Erythrocytes *Am Heart J* 1949 XXXVII 543
- Prinzmetal M Corday E Spritzler R J and Flieg W Radiocardiography and Its Clinical Applications *JAMA* 1949 CXXXIX 617
- Prinzmetal M Simkin B Bergman H C and Kruger H E Studies on the Coronary Circulation II The Collateral Circulation of the Normal Human Heart by Coronary Perfusion with Radioactive Erythrocytes and Glass Spheres *Am Heart J* 1947 XXXIII 470
- Smith, W C and Quimby E H Use of Radioactive Sodium in Study of Peripheral Vascular Disease *Ann Surg* 1947 CXXV 360
- Wright H P Osborne W B and Edmonds D G Rate of Flow of Venous Blood in Legs Measured with Radioactive Sodium *Lancet* 1948 II 767
- Examination of the Blood and Urine (See also references under Blood Flow)**
- Barcroft J and associates "Observations upon the Effect of High Altitude on the Physiological Processes of the Human Body Carried out in the Peruvian Andes Chiefly at Cerro de Pasco *Phil Trans Roy Soc London* 1922 Series B CCXI 351
- Björck G "Myoglobin Its Properties and Occurrence in Man *Acta Cardiologica* 1948 III 223
- Cohen J E and Shock N W Blood Volume Studies in Middle Aged and Elderly Males *Jour Gerontol* 1948 III 5
- Frlanger J "Blood Volume and Its Regulation *Physiol Rev* 1921 I 177
- Fishberg A M *Hypertension and Nephritis* Lea & Febiger Philadelphia 1939
- Gibson J G 2nd "The Clinical Significance of the Blood Volume *Ann Int Med* 1941 XIV 7014
- Goldbloom, A A and Libin I with technical assistance of P K Roht Clinical Studies in Circulatory Adjustments I Clinical Evaluation of Studies of Circulating Blood Volume *Arch Int Med* 1935 LV 484
- Groom D Wood E H Burchell H W and Parker R L "The Application of an Oximeter for Whole Blood to Diagnostic Cardiac Catheterization *Proc Staff Meet Mayo Clin* 1948 XXIII 601
- Henderson L J Bock A V Field H Jr and Stoddard J L Blood as a Physico-chemical System II *J Biol Chem* 1924 LIX 379
- Henderson Y "The Volume of the Circulation and Its Regulation by the Venopressor Mechanism" *JAMA* 1931 XCVII 1,65
- Keith N M Rowntree L G and Geraghty J T A Method for the Determination of Plasma and Blood Volume *Arch Int Med* 1915 XVI 547
- Lindhard J "A Dye Method for Determining the Blood Volume in Man" *Am J Physiol* 1926 LXXVII 669
- Meakins J C and Davies H W *Respiratory Function in Disease* Oliver and Boyd Edinburgh and London 1925
- Milikan C A "Oximeter Instrument for Measuring Continuously Oxygen Saturation of Arterial Blood in Man" *Rev of Scientific Instruments* 1932 XIII 434
- Monge C et al *Estudios Fisiológicos sobre el hombre de los Andes* Facultad de Medicina, Lima 1918
- Morse M Cassels W F and Schultz F W "Blood Volumes of Normal Children Available Interstitial Fluid" *Am J Physiol* 1947 CLI 438
- Reith, A F and Squier T L "Blood Cultures of Apparently Healthy Persons" *J Infect Dis* 1937 LI 336
- Rourke M D and Ernestine A C "A Method for Correcting the Erythrocyte Sedimentation Rate for Variations in the Cell Volume Percentage of Blood" *J Clin Investigation* 1930 VIII 545
- Sadie W C "The Oxygen of the Arterial and Venous Blood in Pneumonia and Its Relation to Cyanosis" *J Exper Med* 1919 XXX 215

- Talbott J H and Dill D B "Clinical Observations at High Altitude Observations on Six Healthy Persons Living at 17 500 Feet and Report of One Case of Chronic Mountain Sickness" *Am J Med Sc* 1936 CXCI 626
- Talbott J H et al "A Record Case of the Tetralogy of Fallot with Comments on Metabolic and Pathologic Studies" *Am Heart J* 1941 XXII 754
- Thomson W A R "The Effect of Potassium on the Heart in Man" *Brit Heart J* 1939 I 269
- Volhard In Mohr and Staehelins *Handbuch der inneren Med* in Berlin 1918
- Wood E H and Geraci J E "Photoelectric Determination of Arterial Oxygen Saturation in Man" *J Lab & Clin Med* 1949 XXXIV 387
- Cardiac Output Blood Flow and Circulation Rate Studies Plethysmography**
- Baer S "The Clinical Application of the Determination of Circulation Times" *Ann Int Med* 1940 XIII 2246
- "The Measurement of the Velocity of Blood Flow" *Mod Concepts Cardiovas Dis* 1942 XI No 1
- Baer S and Slipakoff B G "The Measurement of Circulation Times and the Agents Used in Their Determination" *Am Heart J* 1938 XVI 29
- Barcroft J Bock A V and Roughton F J "Observations on the Circulation and Respiration in a Case of Paroxysmal Tachycardia" *Heart* 1921 IX 7
- Bernstein M and Simkins S "The Use of Magnesium Sulfate in the Measurement of Circulation Time" *Am Heart J* 1939 XVII 218
- Blumgart H L and Weiss S "Studies on the Velocity of Blood Flow II III IV V VII VIII IX X XI The Velocity of Blood Flow in the Systemic and Pulmonary Circulations in Health and Disease" *J Clin Investigation* 1927 IV 15 149 173 194 399 and 555 1928 V 343 379 and 1928 VI 103
- Blumgart H L and Yens O C "Studies on the Velocity of Blood Flow I The Method Utilized" *J Clin Investigation* 1927 IV 1
- Callebaut C Lequime J and Denolin S "Détermination oxymétrique de la vitesse circulatoire chez l'homme" *Acta Cardiologica* 1950 V 137
- Caudel S "Determination of the Normal Circulation Time from the Antecubital Veins to the Pulmonary Capillaries by a New Technic (using Paraldehyde)" *Ann Int Med* 1938 XII 236
- Cournand A Ranges H A and Riley R L "Comparison of the Results of the Normal Ballistocardiogram and a Direct Fick Method in Measuring the Cardiac Output in Man" *J Clin Investigation* 1942 XXI 287
- Donzelot E et al "Valeur de l'épreuve à l'éther pour le diagnostic de shunt veino-arteriel Résultats dans 500 cas de cardiopathies congénitales" *Arch d mal du coeur* 1949 XLII 601
- Elek S R and Solarz S D "The Use of Papaverine as an Objective Measure of Circulation Time" *Am Heart J* 1942 XXIV 821
- Fick A "Ueber die Messung des Blutquantums in den Herzventrikeln" *Sitzungsberichte der phys med Gesellsch zu Wurzburg* 1870
- Friedfeld L Marcus H B and Vorzimer J J "Aminophyllin Determination of Circulation Time" *New York State J Med* 1948 XLVIII 2047
- Gernandt B and Nylm G "The Relation Between Circulation Time and the Amount of the Residual Blood of the Heart" *Am Heart J* 1946 XXXII 411
- Gibbs F A Gibbs E L and Lennox W G "The Cerebral Blood Flow in Man as Influenced by Adrenalin Caffeine Amyl Nitrite and Histamine" *Am Heart J* 1935 X 916
- Goodyer A V N "Observations on the Impedance Plethysmograph" *J Clin Investigation* 1948 XXVII 536
- Greenfield I "Sodium Succinate as a Test of Circulatory Efficiency" *Ann Int Med* 1950 XXXII 524
- Grollman A *The Cardiac Output of Man in Health and Disease* Charles C Thomas, Publisher Springfield Ill 1932
- Gross E "The Measurement of the Lung To-Face Time by Amyl Nitrite" *Am Heart J* 1945 XXX 19
- Gubner R Schnur S and Crawford J H "The Use of CO Inhalation as a Test of Circulation Time" *J Clin Investigation* 1939 XVIII 395

- Hamilton W F et al "Comparison of the Fick and Dye Injection Methods of Measuring the Cardiac Output in Man" *Am J Physiol* 1948 CLIII 309
- Hamilton W F and Remington J W "Measurement of Stroke Volume from Pressure Pulse" *Am J Physiol* 1947 CXLVIII 14
- Hitzig W M "The Use of Ether in Measuring the Circulation Time from the Antecubital Veins to the Pulmonary Capillaries" *Am Heart J* 1935 V 1080
- "The Value of Circulation Times" *Mod Concepts Cardiovas Dis* 1947 XVI No 8
- Hubacher ■ and Nyfleter M "New Method for Determination of Beat Volume of Heart" *Cardiologia* 1946-47 VI 175
- Hussey H H Cyr D F and Katz S "The Comparative Value of Calcium Gluconate, Magnesium Sulfate and Alpha Lobeline Hydrochloride as Agents for Measurements of the Arm to Tongue Circulation Time in 50 Patients with and 50 Patients without Heart Failure" *Ann Int Med* 1942 XVII 849
- Krogh A and Lindhard J "Measurements of the Blood Flow Through the Lungs of Man" *Skand Arch f Physiol* 1912 XXVII 100
- Lisholm E Nylin ■ and Quarns R "The Relation Between the Heart Volume and Stroke Volume Under Physiological and Pathological Conditions" *Acta scand radiol* 1934 XV 237
- M Michael J and Sharpey Schafer E P "Cardiac Output in Man by a Direct Fick Method" *Brit Heart J* 1944 VI 33
- Meneely G R and Chesnut J L "The Relation Between the Size of the Heart and the Velocity of the Blood" *Am Heart J* 1947 XXXIII 175
- Nathanson M H and Elek S R "The Influence of Heart Size on the Circulation Time" *Am Heart J* 1947 XXXIII 464
- Newburgh L H and Means J H "The Blood Flow in a Patient with Double Aortic and Double Mitral Disease (Pioneer study of blood flow in a patient)" *J Pharmacol & Exper Therap* 1915 VII 441
- Norman J K "Reactions to Dechobin in Circulation Time Determination" *Am Heart J* 1947 XXXIV 740
- Nyboer I "Electrical Impedance Plethysmography A Physical and Physiologic Approach to Peripheral Vascular Study" *Circulation* 1950 II 811
- Rung G C Greisheimer E M Bauer H N and others "Electrokymography for Estimation of Heart Output Comparison with Direct Fick in Dogs" *Am J Physiol* 1950 CLXI 231
- Robb G P and Weiss S "A Method for the Measurement of the Velocity of the Pulmonary and Peripheral Venous Blood Flow in Man" *Am Heart J* 1933 VIII 650
- Ross D N "Theophylline-ethylenediamine in the Measurement of Blood Circulation Time" *Brit Heart J* 1951 XIII 56
- Starl I and Schroeder H A "Ballistocardiogram II Normal Standards Abnormalities Commonly Found in Diseases of the Heart and Circulation and Their Significance" *J Clin Investigation* 1940 XIX 437
- Stead E A Jr and Warren J V "Cardiac Output in Man Analysis of Mechanisms Varying the Cardiac Output Based on Recent Clinical Studies" *Arch Int Med* 1947 LXXX 237
- Weiss S Robb G P and Blumgart H L "The Velocity of Blood Flow in Health and Disease as Measured by the Effect of Histamine on the Minute Vessels" *Am Heart J* 1929 IV 664
- Werko L Lagerlof H Buchs H Wehle B and Holmgren A "Comparison of the Fick and Hamilton Methods for the Determination of Cardiac Output in Man" *Scand J Clin and Lab Investigation* 1949 I 109
- Wexler J and Whittenberger J L "Objective Method for Determining Circulation Time from Pulmonary ■ Systemic Capillaries by Use of Oximeter" *J Clin Investigation* 1946 XXV 447
- Wilburne M Schlichter J G Grossman M and Cisneros F "Use of Acetylcholine in Objective Determination of Circulation Time and Fractionation of Vascular Bed Tracer" *Am J Physiol* 1947 CL 504
- Wintemitz M Deutsch J and Brüll Z "Eine klinisch brauchbare Bestimmungsmethode der Blutumlaufzeit mittels Decholinjektion" *Med Abh* 1931 XXVII 986



**Calculation of Work of the Heart and of the Pulse Sphygmobolometry : Energomtry**

- Barach J H "The Energy Index of the Circulatory System" *Am J M Sc* 1916, CLII 84
- Christen T "Neue Wege in der Pulsdiagnostik" *Ztschr f klin Med* 1910 LXXI 39  
*Die dynamische Pulsuntersuchung* F C W Vogel Leipzig 1914
- Evans C L "The Velocity Factor in Cardiac Work" *J Physiol* 1918 LII 6
- Remington J W and Hamilton W F "Evaluation of Work of Heart" *Am J Physiol* 1947 CL 292
- Sahl H "Die Sphygmobolometrie eine neue Untersuchungsmethode der Zirkulation." *Deutsch med Wchnschr* 1907 XXXIII 628

**Functional Tests**

- Bjorck G and Pannier R "One Hundred Positive Hypoxemia Tests" *Nord med* 1947 XXXIII 315
- Brittingham H H and White P D "Cardiac Functional Tests" *JAMA* 1947 LXIX 1901
- Burnett C T Nims M G and Josephson C J "The Induced Anoxemia Test" *Am Heart J* 1942 XXIII 306
- Cabot R C and Bruce H M "The Estimation of the Functional Power of the Cardiovascular Apparatus" *Am J M Sc* 1907 CXXXIV 491
- Hutchinson J "On the Capacity of the Lungs and on the Respiratory Functions with a View of Establishing a Precise and Easy Method of Detecting Disease by the Spirometer" *Medico Chir Tr* London 1846 XXIX 137
- Johnson R E Brouha L and Darling R C "A Test for Physical Fitness for Strenuous Exertion" *Rev Canad d Biol* 1942 I 491
- Leas R D "Vital Capacity: A Study of the Effect of Breathing Dry Air" *Arch Int Med* 1917 XXXIX 475
- Levine S A "The Value of Determination of the Vital Capacity of the Lungs in the Care of Patients with Heart Disease" *Arq brasil de cardiol* 1949 II 253
- Levy H L Barach A L and Bruenn H G "Effects of Induced Oxygen Want in Patients with Cardiac Pain" *Am Heart J* 1938 XV 187
- Levy R L Patterson J E Clark T W and Bruenn H G "Anoxemia Test" *JAMA* 1941 CXVII 2113 and *Am Heart J* 1942 XXIII 837
- McClure C W and Peabody F W "Relation of Vital Capacity of Lungs to Clinical Condition of Patients with Heart Disease" *JAMA* 1917 LXIV 1954
- Master A M "The Two-Step Test of Myocardial Function" *Am Heart J* 1935 X 495
- Montgomery H Naide M and Freeman N E "The Significance of Diagnostic Tests in the Study of Peripheral Vascular Disease" *Am Heart J* 1941 XXI 780
- Scherlis L Sandberg A A Wener J Dvorkin J and Master A M "The Effects of the Single and Double 'Two Step' Exercise Tests upon the Electrocardiograms of 200 Normal Persons" *J Mt Sinai Hosp* 1950 XVII 242
- Schneider E C "A Cardiovascular Rating as a Measure of Physical Fatigue and Efficiency" *JAMA* 1920 LXXIV 1507

---

PART II

THE SIGNIFICANCE, PREVALENCE, CAUSES, AND  
TYPES OF HEART DISEASE

---



---

## CHAPTER 11

---

# THE SOCIAL AND ECONOMIC ASPECTS OF HEART DISEASE

---

**Introduction** The significance of heart disease is far reaching penetrating and affecting the health and happiness work and lives of all peoples on earth and from the cradle to the grave Belatedly the medical profession has at long last taken cognizance of this fact and has begun to enlist the support of patients social groups universities foundations and finally of local and national governmental resources in the growing struggle to elucidate the causes of heart disease and thereby to clear the way for their control

Heart disease or rather cardiovascular disease has become the chief public health problem of our day Ranking as the leading cause of death it has been widely but crudely publicized unwarranted fear of heart disease has swept the country in fact all the world Although it is true that the most recent and most accurate statistics do show a high incidence of cardiovascular deaths three very important considerations counterbalance in large part the seriousness of such a state of affairs In the first place cardiovascular disease or indeed heart disease itself is not just one disease but actually a multitude of different diseases most of which are quite unrelated except as they all involve the heart or blood vessels thus heart disease is very different from tuberculosis or typhoid fever or even cancer Secondly the increase in heart disease is in the older age groups there having been actually a decrease in recent years in heart disease mortality below the age of twenty five in the United States (Hedley 1939) An old person must die eventually of some disease process and a circulatory death is as good to suffer as any indeed probably better than many others Finally many grades of heart disease of various types are contrary to old time tradition mild and relatively unimportant compatible with considerable longevity and full activity

However despite these favorable points about heart disease it still leads other diseases as a cause of death from the age of five years to that of twenty it cripples many thousands of young people as the result of congenital defects and of rheumatic involvement of heart muscle and valves and it strikes down many leaders in professional business and political life in middle age at the

*height of their careers of usefulness* Thus there are many aspects of heart disease that concern society and national economy, in the home in the school in industry in the community and in the nation The present chapter has been newly added to this book in order briefly to discuss these special problems

**Heart disease as it affects the home** Heart disease presents many problems for the home which include the effects both of the chronicity of the condition and of the acute attacks that are so likely to punctuate its course Thus in children there are periods of rheumatic fever often very prolonged which require much patience of the family whether the youngster is in bed at home or away in a hospital or convalescent establishment Since many times in the absence of specific therapy these attacks last for months both child and parents become much depressed and need cheerful medical and nursing care It has been here that expert social service pioneering and recreational therapy when the state of health permits have played in late years an important role At the Massachusetts General Hospital Miss Edith Terry and Miss Lorena Love have established under the aegis of the Committee for the Home Care of Children with Heart Disease the In Bed Club with its badge and jacket and magazine home visiting schoolteachers and occupational therapy have added their share of aid for these children even before they graduate from bed to rejoin their comrades in the usual life of the community Not only are these patients followed in this encouraging manner while acutely and subacutely ill but they and their parents are seen at intervals thereafter to help them from acquiring the attitude so common in the past of resignation to lives of invalidism and fear Often the families need more instruction and building up of morale than do the children themselves And when much schooling is lost it has been found possible by easygoing and well controlled summer courses to promote the child to the class ahead along with his mates In Boston a good additional resource in the care of these children when subacutely ill has been the special foster homes of the Children's Mission when home care proved difficult and hospital attendance impossible or too prolonged

For the mother ill with heart disease acutely in childbearing age or older or chronically disabled the choice of an able and understanding housekeeper is not infrequently more important even than nursing care to relieve both mother and family of undue worry such a person can herself help with the actual nursing too unless the illness is very severe Another problem concerns the need in some cases of limitation of the size of the family and hence of some method or other of birth control expert advice is here often necessary since the risk of childbirth or even of a needed termination of pregnancy should not be countenanced

For the father ill with heart disease the threat of disability and death leaving the family not infrequently inadequately supported requires much careful planning with expert and friendly advice of doctor and business and professional associates It often in fact usually is not necessary for the man with heart disease to retire from his life work except perhaps for a few weeks or

months even after an acute coronary thrombosis. Years ago it was common practice to advise retirement in such a case but fortunately we have learned better in the last twenty five years. Moreover it is wise for a man young or middle aged immersed in his business or professional life to cultivate an avocation or hobby or two not too strenuous to which he may turn with pleasure if in later life he is prevented by illness cardiac or of other sort from continuing his business or professional life or indeed when he retires simply because of age.

Finally there are the elders of the family grandparents and great grandparents who may have heart trouble the commonest ailment of the aged. They may be a great burden for their juniors not only medically but socially and financially as well especially if they perforce reside with them. Much better planning in the future will be needed than in the past to help solve this difficult problem especially since there will be constantly more and more old people in the world. They themselves must plan better for their future when they are young their families must acquire a better attitude toward their elders with the respect for age that has been the Chinese tradition and finally the medical profession and the community itself must devote more time and interest to this problem of the care of old age which has been variously called gerontology and geriatrics a special field that will one day rank in interest and importance with pediatrics.

**Heart disease as it affects the school.** The youngest school children five and six years old may have heart disease either congenital or the beginning of rheumatic. In fact these troubles may delay their entrance into school life by a year or more either because of the severity of the symptoms of the morbus caeruleus or because of active rheumatism which may be severe and prolonged at this early age and require months of bed rest. Except for these two conditions however most children with heart disease at any age can safely and profitably attend school and need not in fact should not be separated off in special categories or classes except for rare individuals who are unusually crippled by early and marked valvular deformity cardiac arrhythmias or congenital defects of noncyanotic type. It has not been found necessary to establish as at one time was planned special cardiac classes in the public schools. Happily however in many communities home visiting is carried out by public and private schoolteachers when the children are well enough to receive them thus keeping up both instruction and morale. And when the children do get back to school there is often a sensible arrangement whereby they may be watched and guided without making them overanxious resentful or set apart to do this there can wisely be a cooperative plan of schoolteachers parents and family doctor.

The instruction itself in the upper classes in the teens can be skillfully directed toward an interest in sedentary occupations later in life if there is much heart trouble but often there is so little wrong (as for example slight mitral valve deformity or a small ventricular septal defect) that there need be no restrictions whatsoever present or future. The same principles apply to

athletic sports and gymnastic exercises. Infrequently it is necessary to curtail them but often it is wise to direct a child to baseball in preference to basketball, hockey or football and to short races and jumping in preference to marathon runs, crew races, distance swims and heavy skiing.

Most important of all in these various considerations is the individual himself. No two patients are exactly alike and so it is vital to decide about every case on its own merits.

Heart disease as it affects industry, business, and professional life. In the past there has been much unnecessary fear of heart disease in its relationship to industry but happily a saner attitude is now developing as the result of informing the public at large of the accumulating experience of the medical profession. During the last generation it has become quite evident in the first place, that the majority of persons with heart disease live a good many years after its onset; in the second place, that the great majority of such long survivors can live useful and contented lives; and finally that they are with uncommon exceptions benefited rather than harmed by work to which they are accustomed for which they have been trained and which they enjoy. Far too many cardiac invalids have resulted from the oversolicitous attitude of family friends or even physicians themselves and from the apprehension of industries, businesses and professional associates and clients. A recent survey of opinions of experts of the American Heart Association Committee of the Effect of Strain and Trauma on the Heart and Great Vessels has confirmed the experience of the author in this respect, namely that the routine activity of persons in industry, business and the professions if carried on in a sensible manner neither initiates heart disease nor makes it worse if it is already present unless it is very severe or going through an active stage as in the case of acute rheumatic carditis, of acute or subacute coronary insufficiency or of myocardial insufficiency. Under the conditions of such complications omission of work and rest at home or in hospital are of course indicated but often only temporarily for after these conditions have cleared up many persons can safely resume work to advantage to both morale and physical health to say nothing of their economic status in the support of themselves and of their families.

One must of course separate off from the routine strains of industry, business and the professions accidents and trauma, physical or mental which can occur just as often at home or at play or in the crowded traffic of the present day (see Chapter 23). As a matter of fact, acute coronary thrombosis and deaths from angina pectoris and cerebral vascular accidents are much more likely to occur away from work than on the job and often even in bed. There should be a clearer understanding by industry and more widespread satisfactory insurance laws to meet the problem of the person with heart disease than have existed in the past. One of the pioneers (Dr Irvine Clark) in this regard who has had experience over many years in the employment of cardiacs in industry has emphasized the value and safety of so doing slowly, this word is getting about. Of course there must be safeguards

such as a careful appraisal of the individual at the beginning an examination annually or oftener if the need arises and proper treatment when complications come as they may whether the person is working or not. Industry should not be blamed for such complications any more than some trivial accident which may have brought to light heart disease which has existed for years. On occasion some unusual strain or trauma may expedite a complication and if so a justifiable and satisfactory attempt can be made to apportion the responsibility of such an exciting factor in the overall picture for example in a patient with a moderate or considerable degree of mitral stenosis some special strain may set off atrial fibrillation which might not have come on otherwise for some weeks or months or even a year or two but such strain should not be considered as 100 per cent responsible for the temporary disability that results it may not rate more than 10 per cent.

These remarks apply to every kind of heart disease even the morbus caeruleus but of course youngsters with severe congenital or rheumatic heart disease should be trained in their youth for sedentary occupations and oldsters may need to reduce their time at work or sit instead of stand or shift to another job. With regard to changing occupations one should add that a somewhat active job for which a person is trained at which he or she is skillful and which is well liked may afford actually far less strain than a new job which seems easier physically but which may prove both difficult and boring for the person concerned. Thus one must individualize advice for every case lists of occupations for 'cardiacs' may be somewhat useful but they are only rough guides at best.

We should not deprive our cardiac patients of education or some sort of occupation just because they seem hopelessly handicapped. A good lesson in that respect was taught by a patient of mine with a high degree of the tetralogy of Fallot who because of much cyanosis and delicate health in early childhood received no schooling at the advice of the doctor in attendance because it was thought that such would be a waste of time and money. However by good care and good luck he lived to be sixty years old but more important still by sheer will power and genius he educated himself to be one of the leading musical composers of his generation.

**Heart disease as it affects the community** Much that has been discussed under the headings of home school industry business and the professions naturally applies to the community as a whole but there are other aspects of the community that deserve mention. One is that of the general standard of living. Where there is a low average level heart disease like a good many other diseases is more common. It is well known for example that rheumatic heart disease is twice as common in the poorer more crowded sections of a city than in the suburbs where living conditions are better. Much the same statement is true about cardiovascular syphilis only still more so. Also the circulatory diseases of middle age both peripheral and cardiac are more subject to neglect under poorer conditions of living. We do not as yet however have an adequate statistical appraisal of their varied incidence and it



may be that the overnutrition that is more likely to prevail among the well-to-do has its influence in the etiology or at least aggravation of the so-called degenerative diseases such as coronary atherosclerosis and hypertension. A community sense of responsibility for health conditions builds up slowly but eventually leads to the establishment of a proper health agency in close harmony with private practitioners, hospitals and medical schools. Some small communities in the country today lack physicians close at hand; they should join others in similar plight or perhaps better situated to set up some central group or hospital where someone trained in the field of cardiovascular disease can be available, as in other specialties with essential equipment such as electrocardiograph and fluoroscope.

**Heart disease as it affects the nation** Next to last we come to the problem of the national health. That statistically so far as the heart is concerned will be dealt with in the next chapter but there are a few additional comments to be made here. In the first place heart and peripheral circulatory diseases are by far the most common causes of death in the U.S.A. today and so naturally they hold the limelight in the current national health program. Fortunately both public enterprise via the new National Heart Institute and National Advisory Heart Council established by act of Congress in 1948 and private enterprise headed by the American Heart Association organized in 1924 are working in close harmony in the support of research and teaching in the field of cardiovascular disease. Happily research has the priority for it is evident that the sooner we discover and thereby learn to prevent the underlying causes of heart disease the sooner we shall rescue our young people and middle aged population from cardiac invalidism and death and the less effort, time and money we shall need to plan for and expend in their care. An increasing mortality from heart disease per se in the years to come need cause no alarm in fact such may be welcomed provided death comes quickly, comfortably and quietly while at rest in bed or easy chair at an advanced age say at ninety after a long and happy and useful life. But there is still tragedy in the newspaper headlines on occasion when some notable and public spirited citizen suddenly succumbs to heart disease in the very prime of life and at the top of his career.

**Heart disease internationally** Finally the problem of heart disease is world wide and what has been said about its community and national relationships applies equally to all nations. An International Cardiac Council was organized in Mexico City in 1946 to help to correlate the various national activities in the cardiovascular field and to aid in setting up the first International Cardiac Congress in Paris in the fall of 1950. At that congress there was established the International Society of Cardiology (Heart and Blood Vessels). There are herein many opportunities for future cooperative researches in the incidence and etiology of heart disease throughout the world and in the strengthening of international medical friendship.

## BIBLIOGRAPHY

## SOCIAL AND ECONOMIC ASPECTS OF HEART DISEASE

- Bellevue Hospital The Staff of the Work Classification Unit Adult Cardiac Clinic An Occupational Analysis of 580 Cardiac Clinic Patients *Circulation* 1951 III 289
- Clark W I Jr Heart Disease in Industry *Boston Med and Surg J* 1922 CLXXXVII 21
- Conner L A The Rehabilitation of Cardiac Patients Through Organized Effort *JAMA* 1927 LXXIX 496
- Cowdry E V *Problems of Ageing Biological and Medical Aspects* Williams & Wilkins Co Baltimore 2nd ed 1942
- Dawber T R Meadors G F and Moore F E Jr Epidemiological Approaches to Heart Disease The Framingham Study *Am J Pub Health* 1951 XLI 279
- Dolgin M Grossman M Simon A J Sorter H and Katz L N Cardiovascular Survey of Residents in a Custodial Institution for the Aged *J Gerontol* 1949 IV 39
- Dublin L I "Heart Disease and Public Health" *Am Heart J* 1942 XXIII 16  
Public Health and Disease of Old Age (Summary) *Statistical Bull Metropolitan Life Ins Co* 1948 IX 1
- Dublin L I and Lotka A J *Length of Life A Study of the Life Table* The Ronald Press Co New York 1936
- Dunton W R and Licht S *Occupational Therapy Principles and Practice* Charles C Thomas Publishers Springfield Ill 1950
- Editorial The National Conference on Aging *JAMA* 1950 CXLIV 46
- Emerson H Economic Aspects of Heart Disease *Am Heart J* 1929 IV 251
- Hedley B F Trends Geographical and Racial Distribution of Mortality from Heart Disease Among Persons 5-24 Years of Age in the United States During Recent Years (1922-1936) *US Pub Health Rep* 1939 LIV 2271
- Kattwinkel E E Getting V A Morris E M Lombard H M and Robbins L C A Public Health Heart Program First Report *New England J Med* 1949 CCXLI 446
- Kossmann C E Goldwater L J and de la Chapelle C E Selective Placement of Patients with Heart Disease in Competitive Employment *Am Heart J* 1947 XXXIII 700
- National Heart Act. U S Public Law 655—80th Congress (Chapter 481—nd Session) (S 215) 1948
- Probst E W "Employment of Hypertensives in Industry" *Indust Med & Surg* 1949 XVIII 462
- Shepard W P The American Heart Association as a National Voluntary Public Health Agency" *Circulation* 1950 II 736
- Sprague H B Mental Adjustments to Heart Disease The Factors Involved in Disability" *JAMA* 1939 CXII 2384
- Ungerleider H E and Gubner R "Insurance Aspects of Heart Disease" *M Clin North America* 1950 XXXIV 805
- U S Public Health Service New Clinical Center for Medical Research *JAMA* 1951 CXLVI 668
- White P D The Problem of Heart Disease in the Industrial Worker" *J Indust Hyg* 1921 III 219
- Heart Disease A World Problem *Bull New York Acad Med* 1940 XVI 431
- "The Reversibility of Heart Disease" *Illinois M J* 1944 LXXXVI 9
- Wyckoff J "The Organization of the Cardiac Clinic" *New York State J Med* 1925 XXV 994

## PREVALENCE OF HEART DISEASE AND OF ITS ETIOLOGIC TYPES

---

**The frequency of heart disease** The first aspect of the prevalence of heart disease to be considered is that of its total frequency though actually this is much less important than a second aspect to be considered later namely that of the relative and absolute frequency of the various kinds of heart disease dependent on the various causes. Accurate information about either the incidence or the prevalence of heart disease in the community is as yet scarcely available anywhere in the world this information is obviously of great importance and much work remains to be done in securing it. We possess scattered data of small or limited scope or of uncertain reliability from a number of sources data which are largely incomplete or otherwise unsatisfactory. These sources include life insurance statistics periodic health school industrial athletic and military examinations and hospital and mortality figures.

The estimation of community prevalence of heart disease has varied from less than 1 per cent to several per cent. The reported results of examination of school children have differed widely, but reasonably satisfactory studies in the northeastern part of the United States have indicated that nearly 1 per cent of children of school age have organic heart disease while in San Francisco only 0.37 per cent of cardials were found among the school children one half or more of whom had congenital heart disease (Sampson et al 1938) and in Cincinnati the figure was midway 0.53 per cent with 55 per cent of them rheumatic and 45 per cent congenital (Rauh 1939). In 1946-47 Robinson and his associates found among the San Francisco school children 0.44 per cent of cardials which when further analyzed, showed 0.24 per cent rheumatic heart disease and 0.19 per cent congenital heart disease. However rheumatic heart disease was not at all rare among the children of South California some ten to fifteen years ago as indicated by the finding of 3 per cent of cases at autopsy at the Children's Hospital in Los Angeles among patients through 14 years of age. Eighty per cent of the cases at the Children's Hospital were California born (Thompson personal communication 1949).

At the Children's Hospital in Boston in 1949 1.3 per cent of the autopsied cases showed rheumatic heart disease and 10 per cent congenital (there were many infants)

The prevalence of heart disease in school children varies very much with climate because of the greater frequency of rheumatic heart disease in cold wet and high altitude areas for example Sampson et al (1945) reported 2.04 per cent rheumatic heart disease among the school children of Eureka in the extreme northern end of California in contrast to 0.32 per cent of rheumatic heart disease among the school children in Redlands in the extreme southern end of California. The incidence of congenital heart disease was approximately the same in both places—0.07 per cent in Eureka and 0.08 per cent in Redlands. In 1945 Wedum et al reported among school children in Denver 1.63 per cent with rheumatic heart disease.

Among 28,139 young adults entering the University of Wisconsin between 1931 and 1939 there were 289 cases (1 + per cent) of heart disease with sex ratio of 1.7 females to 1 male (Cole 1941). From middle aged adult examinations and from the certainty that in old age the incidence of heart disease is very much higher than in youth it may be stated as probable that at least 2 per cent of the total population of the northern part of the United States have heart disease of a degree sufficient to produce symptoms or signs.

As a cause of death heart disease has assumed greater and greater proportions in this part of the world until now it leads all other causes having far outstripped tuberculosis pneumonia and malignant disease the other three most common fatal diseases and also outnumbering accidental deaths which now rank in third place as a cause of death. This increase which is absolute as well as relative is due to several reasons: the individual importance of which is not yet known: (1) more accurate cardiac diagnosis; (2) fashions and revisions of recording diagnoses (for example coronary artery disease was classified some years ago under the heading of arterial disease in the Massachusetts state records while now it is classified under the heading of heart disease; most persons formerly diagnosed as having Bright's disease are now recognized properly as having hypertensive heart disease with congestive failure and not primarily kidney disease and many persons who died of old age years ago would now be recorded as having died of cardiovascular disease); (3) reduction of incidence of certain other diseases especially of infections like infantile dysentery tuberculosis and typhoid fever with a corresponding increasing ratio of heart disease deaths; and (4) actual increase of heart disease due in part at least to this very same decrease in mortality from other diseases. Some individuals who in former days would have died of dysentery in infancy of diphtheria in childhood, or of tuberculosis or typhoid fever in early adult life now die of rheumatic syphilitic hypertensive or coronary heart disease instead. See Table 2 and Figure 57.<sup>1</sup>

<sup>1</sup> It is with much appreciation that I acknowledge the valuable assistance of Mr Felix E. Moore Jr., chief of the Biometrics Research Section of the National Heart Institute Bethesda Md. in the revision of Table 2 and Figure 57 and for other helpful advice about this chapter.

As a background for the increasing mortality from heart disease it is of interest to cite the decreasing death rate in the United States in 1900 the death rate from all causes in the registration states was 1,719 per 100 000 in 1910 it was 1 468, in 1920 it was 1 299, in 1930 it was 1 132 in 1940 it was 1 074 in 1945 it was 1 062 and in 1948 it was 988 The figures for Massachusetts are given in Table 4 It is of much interest that mortality from epidemics has been on the decline in late decades Except for the one serious

Table 2

## MORTALITY STATISTICS FOR MASSACHUSETTS, 1900 TO 1945

(Cases allocated to place of residence since 1935)

Year	Death rate per 100 000 population				Total death rate per 1 000 population	Infant death rate per 1 000 live births
	Diseases of the Heart	Cancer	Tuberculosis (all forms)	Pneumonia (all forms)		
1900	165	75	214	172	18.4	*
1905	196	89	192	153	16.7	*
1910	200	91	164	175	16.1	*
1915	201	103	119	159	14.3	101
1920	215	115	114	156	13.8	91
1925	248	124	83	118	12.4	73
1930	282	136	64	93	11.6	60
1935	336	148	46	89	11.5	48
1940	412	169	38	58	11.8	38
1945	447	187	39	49	12	37

Source: National Office of Vital Statistics

\* Not available on comparable basis before 1915

epidemic of influenza at the end of World War I there have been no increases in mortality from epidemic disease since the beginning of the twentieth century (see Figure 58 for Baltimore)

In previous editions of this book it was stated that approximately one out of every three or four deaths in the USA at large and in individual areas (such as the State of Massachusetts) was due to heart disease but steadily the proportion has risen so that now if we include all the ramifications of cardiovascular disease including for example renal vascular disease the ratio is very close to one out of two (49.5 per cent) Figure 59 illustrates well the recent data

The accuracy of death certificates is still subject to great improvement but it has gained rapidly during the last generation That the increasing percentage of cardiac deaths is not a unique feature of this country is shown by statistics recently received from France in Lyons from 1887 to 1891 deaths caused by heart disease made up 7.7 per cent of total deaths from known causes while from 1938 to 1940 they made up 17.3 per cent in large part apparently because of the reduction in mortality from other diseases since the actual number of cardiac deaths did not increase proportionately (Paris letter February 7, 1942 JAMA 1942 CXVIII 1155) This very increase in

mortality from heart disease provided it comes in old people may be a source for congratulation rather than dismay since it means that life is now being limited by the degenerative lesions of old age rather than by the infections of youth. But such degenerative lesions should not appear in youth or middle age. The relationship of morbidity and mortality to age is thus a vital one in any consideration of statistics of public health. See Figures 60 and 61 on pages 271 and 272.

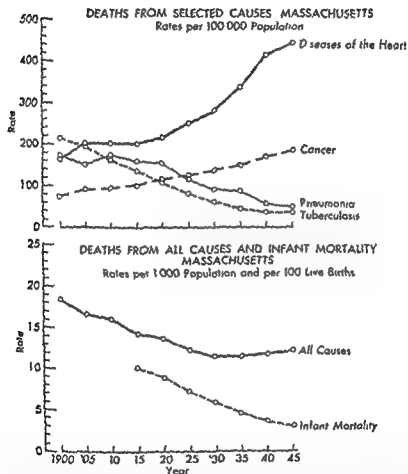


FIG 57 Death rates from diseases of the heart cancer tuberculosis and pneumonia and death rate from all causes and infant mortality rate Massachusetts 1900-1945

It is of great interest that the average duration of human life has more than doubled in the United States of America in the brief interval since its establishment 165 years ago. It has been estimated that the average duration of life in this country in 1790 was about 30 years; in 1930 it was 58.8 for white men and 62.4 for white women; and in 1947 65.16 for white men and 70.54 for white women. This greater longevity of females has been con-

sistently 4 to 5 years for many decades (Dublin 1933 1941—*Statistical Bull. Metropolitan Life Ins Co* 1949 XXX No 10) The expectation of duration of life among the Negroes in the United States in 1930 was 13 years less than that among the whites in 1947 it was reduced to 8 years In 1911 among the policyholders of the Metropolitan Life Insurance Company the expectation of life was 46.6 years and in 1949 less than four decades later it was 67.8 years In some parts of the world where infant mortality and youthful infections are still high the average duration of life is still only in the twenties about as it was probably in Europe in the Roman Era and in

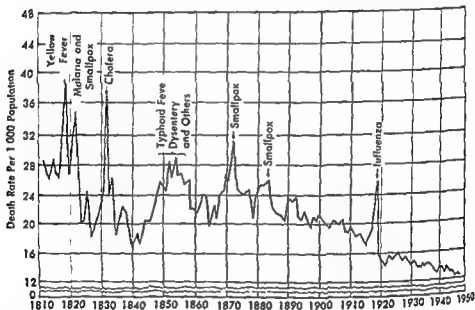


FIG 48 Annual death rates from all causes with indication of principal epidemics, Baltimore, Maryland 1812-1948 (Kindness of the Metropolitan Life Insurance Company, New York)

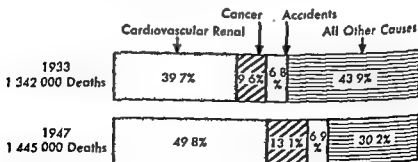


FIG 49 Proportionate mortality from leading causes of death in the United States of America 1933 and 1947 showing the increasing death rate from cardiovascular renal diseases (Kindness of Mr. Felix E. Moore Jr., National Heart Institute, U.S. Public Health Service, Bethesda, Md.)

the Middle Ages (Figure 62) However despite the wonderful increase in the average duration of human life in this country in the past century or so the expectation of life for the man or woman who reaches 60 years is no greater now than it was years ago and probably a little less this is a very important aspect of the subject that should receive increasing attention in the future The longest lived persons (centenarians) are in the main those who with a good family inheritance of longevity have lived physically active lives in rural surroundings

Other relationships of morbidity and mortality from heart disease of great importance besides absolute and relative frequency and age are those to

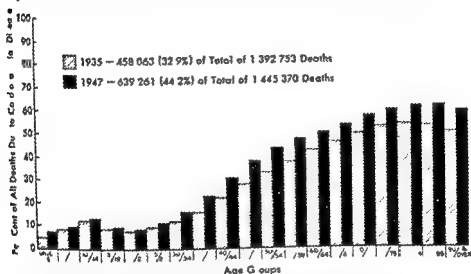


FIG 60 Chart showing total mortality from cardiovascular diseases as compared to all other causes according to age groups in the United States 1935 and 1947 (Kindness of Miss Marjorie Bellows American Heart Association New York City)

climate race heredity sex and social and financial status Favorable influences in reducing the incidence of heart disease in young as well as old are mild dry climates good but not rich food moderate physical exercise and healthful uncrowded living conditions Recently it has been noted that a good environment seems to be more important than having long lived parents in determining the individual's prospect for long life (*Statistical Bulletin Metropolitan Life Insurance Company* February 1942 XXIII No 2) The importance of heredity in cardiovascular disease however is very great perhaps as great as or greater than any other factor but its exact significance remains obscure It has also been found that race is sometimes an important factor Negroes showing twice the prevalence of heart disease as do whites Sex is concerned in three respects in the first place there seems to be a law of nature throughout the entire animal kingdom from insects up to man that the male is considerably shorter lived than the female secondly sex affects the prognosis in every variety of heart disease males living usually a shorter time with any



given heart disease than females, probably in part because of the greater burden imposed by the more active life and thirdly it is related somewhat to the various etiologic types rheumatic heart disease and heart trouble from thyrotoxicosis being found more often in females and coronary heart disease and cardiovascular syphilis more often in males. The whole problem of the incidence of heart disease needs however much further study.

The causes of heart disease. The second and the most important aspect of

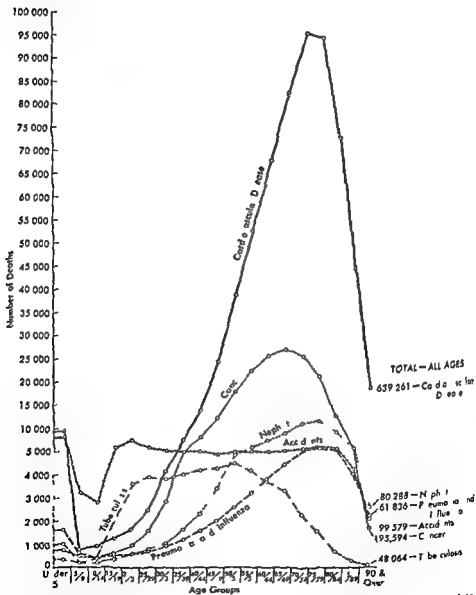


FIG. 61. Chart showing total mortality from cardiovascular disease as compared to all other causes according to age groups in the United States 1947 (Kindness of Max Marjorie Bellows American Heart Association New York City)

heart disease is that of its causes and their relative frequency. With the developing interest in preventive medicine in recent years there has come the realization of the need of analyzing all disease from the etiologic standpoint. Since heart disease is the source of much illness and of high mortality in nearly every community it has attracted much attention and efforts have been made to determine the relative and absolute importance of various factors thought responsible for heart symptoms and signs. Preliminary classification of causes and etiologic types of heart disease has begun in several communities. It holds much promise for the future for it is only as we see the importance of etiologic factors of disease that we can view them in due proportion and concentrate our efforts toward the eradication not only of the most

AVERAGE LENGTH OF LIFE FROM ANCIENT TO MODERN TIMES

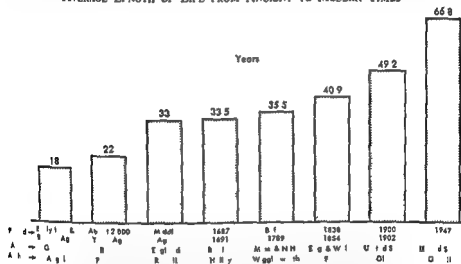


FIG. 67 Chart showing the expectation of life from ancient to modern times (Kindness of Dr. Louis I. Dublin, Metropolitan Life Insurance Company, New York. Published in *Length of Life*, Ronald Press Company, New York, 1949.)

serious pathologic states but also of those most amenable to such an attack in the current state of our knowledge.

It is evident that although investigation of many causes of heart disease may well be carried on at the same time by workers all over the world the wisest course is to concentrate in any one community on that community's own particular causes most in need of control or most obviously open to attack. In New England the rheumatic infection, hypertension, and presenile coronary disease are the most important factors now demanding study. Many years will elapse before we are left with the problem of old age alone. Meanwhile the practitioner of medicine may himself contribute to the progress either by concentrated study of some particular etiologic factor or factors or, in a routine way, by recording as accurately and faithfully as possible in every patient with heart symptoms or signs the causes, whether clear, doubtful, or

unknown. Gradually in this way will come a better realization of the problems which lie before the medical profession in this large and important field.

Lest it be thought that the effort of classifying each cardiac patient according to etiologic type is superfluous or an idle fancy of a public health Utopia I would hasten to add that for the individual patient himself the method is also of great value. Accurate diagnosis, prognosis and treatment may depend entirely on the recognition of the cause of trouble. It can definitely be said that the etiologic diagnosis is often more important than that of either structural change or functional condition. Congestive failure (myocardial insufficiency) and angina pectoris (coronary insufficiency) are of course of prime importance to recognize and treat as functional disorders, but we can handle these cases much more intelligently if we know the fundamental cause of the disease back of their insufficiency. For example, congestive failure complicating coronary occlusion is more serious as a rule than that due to chronic mitral stenosis, and angina pectoris in syphilitic aortitis is more significant than that in rheumatic aortic regurgitation in youth or in mild form in the coronary disease of old age.

There are changing fashions in medical diagnosis. A generation or two ago it was considered sufficient to ascertain the pathologic alterations present in the way of structural damage in the heart, and textbooks were filled with a discussion of valvular lesions and myocarditis. Then came a step forward when greater emphasis was placed on the functional state of the circulation than had been done before (Mackenzie 1908). This emphasis was much needed and served an important purpose, but there has been a strong tendency as a result to make too light of the structural defects and indeed hardly to bother to look for them in detail. The pendulum swung too far, but there is now fortunately reappearing a growing respect for the lesions in the heart that can themselves serve as sources of strain and failure, or that point to other disease processes or to other sources of strain in the body. We must not think too little of either functional disorders or structural changes; we must seek them all and make note of them, at least those of most importance in cardiovascular diagnosis. A functional disorder like paroxysmal tachycardia sometimes may be alarming, but it is usually unimportant and far less significant in diagnosis than is mitral stenosis. On the other hand, a slight chronic rheumatic aortic regurgitation is far less important than is the serious functional disorder of angina pectoris.

It is with the newest element of cardiac diagnosis, the etiologic factor, that this part of the book will deal. This element has long been more or less recognized as of some importance, but only in the last generation has it been emphasized properly (Cabot 1914). The following quotation represents a milestone in the progress of our study of cardiovascular disease.

Cabot R. C. The Four Common Types of Heart Disease. *JAMA* 1914 LXIII 1461.

To classify cases of disease according to their pathogenic agent or process

and not solely by naming the region affected or the function disturbed in the ideal of scientific progress in medicine

"But until the last decade we have made little advance in this direction as regards the diseases which gravely disturb heart function. Thus we still find in standard textbooks a section devoted to mitral regurgitation: its diagnosis, prognosis and treatment, although mitral regurgitation is almost as vague a phrase as spinal paralysis or brain fever. Just as a spinal paralysis may be due to trauma, to the tubercle bacillus, to the *Spirochaeta pallida*, to the organism of poliomyelitis or to cancer, so mitral regurgitation is only a symptom caused by the action of streptococci, by the degenerative lesions of arteriosclerosis, by the muscle tiring resistance of nephritic hypertension and probably by many other causes.

"A similar criticism applies to all diagnoses of myocarditis. The micro organism of rheumatism and of syphilis, the ravages of arterial disease and perhaps many other causes may produce the lesions of chronic fibrous myocarditis, with or without recognizable symptoms. A diagnosis of myocarditis is like a diagnosis of ulcer: it calls for an etiologic qualification, such as syphilitic or tuberculous.

"The matter has many practical aspects. A sane prognosis and treatment of aortic regurgitation, for example, depends on knowing or guessing what disease has produced it. Even physical diagnosis may have to await an intelligent interpretation of its results until we make up our minds what micro organism is at work in the heart, as well as elsewhere in the body.

While we should thus emphasize etiology and consider it first and generally foremost, we must not lose sight meanwhile of the other two legs of the tripod of cardiac diagnosis: structural change and functional condition. All together the three elements complete satisfactorily our modern idea of analysis of a cardiac case. This represents another step in our progress and a sound one built upon the experience of the past and of the present. Instead of diagnosing simply mitral stenosis or atrial fibrillation or rheumatic heart disease in a given case, we should make the complete diagnosis of rheumatic heart disease (etiologic) with mitral stenosis (structural defect) and atrial fibrillation (disorder of function). (White and Myers 1921)

Heart disease may be very complicated. Not only are there many different causes of trouble, but two or more of these separate causes may occasion trouble simultaneously in the same heart and in different and even inconstant degrees. Often much study and discernment are necessary to judge the relative responsibilities of several different causative factors in a given patient and in some cases it may be impossible to unravel the tangle. In this volume the combinations of etiologic factors that are most common or important will be indicated in the discussion of complications in each chapter.

In the present part of the book the more important causes and etiologic types of heart disease will be given by chapters chiefly according to age prevalence, since that is a very practical arrangement, leaving for later consideration certain factors of but slight or doubtful importance or of extreme rarity. This plan seems better than that of arrangement according to importance or frequency, because it leads one chronologically through the life history of man and because the various factors are of different prevalence and importance in

Table 3—THE RELATIVE PREVALENCE OF THE VARIOUS ETIOLOGIC TYPES

Etiologic Types of Heart Disease		USA (as of alphabetical)															
		Alabama, 1912-1914 White males, 15-44		California (San Francisco), 1913-1916		Colorado, Denver, 1913-1916		Illinois, Cook County Hospital, 1913-1916		Iowa, 1913-1916		Kentucky, 1913-1916		Louisiana, 1913-1916		Maine, 1913-1916	
Cognate		11.5		22.3		17.0		19.0		27.0		13.0		11.0		10.0	
Infectious	Rheumatic type	11.5		22.3		17.0		19.0		27.0		13.0		11.0		10.0	
	Subacute bacterial endocarditis	0.2		0.9		5.4		1.9		1.0		.85		.35		.11	
	Acute bacterial endocarditis	0.2		0.9		5.4		1.9		1.0		.85		.35		.11	
	Cardiac sarcoid	0.9		7.0		2.6		27.1		3.0		2.33		1.34		.70	
	Other, including diphtheria, scarlet fever, etc.	0.9		7.0		2.6		27.1		3.0		2.33		1.34		.70	
Thyroid disease		2.9		0.5		3.0		1.6		1.5		.4		.01			
Hypertension	Systemic Hypertension	55		21.5		30.4		53.6		24.5		12.35		35.5			
	Pulmonary Hypertension	0.9		0.9		0.9		1.1		.02		.04		1.5			
Coronary atherosclerosis (including cases with angina pectoris)		3.8		3.6		17.3		21.1		12.5		12.3		25.9			
Miscellaneous—Tuberculosis, etc.		3.5		6.8		6.4		1.3		1.0		1.0		—			
Unknown		1.0		1.4				2.3		4.5		—		—			

†Excluded those cases with hypertension

# OF ORGANIC HEART DISEASE IN CERTAIN PARTS OF THE WORLD

150	79	070	240	151	120	130	110	100	90	80	70	60	50	40	30	20	10	0
37.5 hosp per 100	23.8	43.8 25.5	27.2	15.1	12.0	13 11	20.0	44.0	15.1 4.3	10.4 3.0	1.8 1.2	9.2 31.0	14 1.2	45.3 50.5	24.0 6.3	14 1.2	56.3	26.0 13.3
19	12	-0.5	-	3	130 hosp per 100	-	-	0.2	-	-	-	-	-	-	-	-	-	-
Ra	Ra	-0.5	-	1	hosp per 100	-	-	-	-	-	-	-	-	-	-	-	-	-
29	10	9.3 3.0	4.6	8.5	5	4	2.0	1.1	13.4	31.0 12.7	-	-	-	-	-	-	-	-
Ra	R	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
29	0.5	1.1	-	1.1	-	-	2.0	9.3	-	-	-	-	-	-	-	-	-	-
29.2	26.2	1	20.1	33.4	27.6	70 38	49.4	14.9	65.1 71.8 mb ed	45.3 50.5 37.2	-	46	44.9	-	-	-	-	-
0.9	1.1	0.5	-	6.2	-	17 21	20.3	21.1	-	24.0 6.3 20.2	-	46	9.3	-	-	-	-	-
3.7	48.5	18.4 43.5	8.8	22.4	51	-	-	-	-	-	-	-	-	-	-	-	-	-
21	17	0.1	-	4	94	-	-	0.9	-	14 1.2	-	-	-	-	-	-	-	-
34	0.6	19.5 8.1	-	24	-	-	5.6	7.3	-	56 4.1	-	2	-	-	-	-	-	-

19 5 pe t f th pr t pat t h d g pe t n d only 91 pe nt of th hospital case

Table 3—Continued

Etiologic Types of Heart Disease		Slavovitch, H. A. <i>et al</i> (1940) 81,949 medical examinations	Petersen, R. O. <i>et al</i> (1943) (1937-1944)	OTHER COUNTRIES (estimated alphabetically) Ascertainment: 1943-1944 10,000 adult patients (6,000 hospitalized, 4,000 per cent)	Consolidated (1943-1944) 4,000 cases (3,000 hospitalized, 1,000 per cent)	C. J. A. <i>et al</i> (1943) 3,594 cases (2,279 hospitalized, 213 per cent)	B. A. <i>et al</i> (1943) 438 cases	Best, J. N. <i>et al</i> (1943) 3,664 patients (1,100 cases)
Congenital anomalies		37	10	24	25	15	15	361
Infect	Rheumatic type	173	174	182	184	230	93	113
	Subacute bacterial endocarditis	18						
	Acute bacterial endocarditis							
	Chronic rheumatic	22	61		90	68	142	135
	Other (bacterial, fungal, etc.)	23						
Thrombotic		35	6	58	35	12	11	
Hypertension	Systemic Hypertension	322 Hypertension 6.8%	228	23	200	230	452	215
	Pulmonary Hypertension	23		37	16	69		
Coronary atherosclerosis (arteriosclerosis)		33	399	296	364	396	269	313
Miscellaneous (all other types)		17	102	89	88	20	13	168
Total		15					4	

B3 personal communication with Cassi (1943)





different parts of the world In New England for example rheumatic heart disease makes up an imposing percentage of all types put together and syphilis as a factor is relatively unimportant, while among the Negroes in the South rheumatic heart disease is far less common and cardiovascular syphilis far more frequent It is still too early to give satisfactory figures for the prevalence of etiologic types in different parts of the world only a few studies have been made which allow certain comparisons and these are not always parallel The surface has hardly been scratched A large amount of international cooperative research along these lines deserves early priority

I have tabulated on pages 276 to 279 the etiologic types of heart disease listed according to age incidence which may be found helpful as a guide to further study In this list will be found figures of percentage prevalence of the various types reported from New England New York Washington DC and several states of the South Middle West the Rockies and Far West in the United States and from England Norway South Africa Colombia Mexico the Argentine India, and the high seas The figures are often inadequate and of limited value but they are the best we possess today slowly they are increasing in number and accuracy (see Table 3 pages 276 to 279)

Finally we must at present leave a space in our classification entitled 'of unknown cause' this is still an important group varying in different localities from about 1 or 2 per cent up to 15 or 20 per cent This very acknowledgment of our ignorance should act as a spur to us in our studies until eventually we may be able definitely to say we do know all the causes of heart disease With that knowledge there is bound to come more opportunity to prevent heart disease Incidentally there is an enormous miscellany of diseases which may depress the circulatory function or slightly or terminally alter the heart or the blood vessels (see the end of Chapter 23) but which do not deserve the designation of types of heart disease

To add important and useful information about heart disease in order to help fill the many and serious gaps in our knowledge has required the concentration of many workers in the past three or four decades especially since World War I (1914-1918) These men and women who have become specialists in this field have advanced our knowledge about cardiovascular disease further in that short interval of time than it had traveled in all the centuries that had gone before when few doctors had the interest or took the time to study the heart and circulation either in the normal man or in the cardiac patient This book which is largely a record of the work of the hundreds of students and investigators of cardiovascular disease since 1900 is a testament to that truth

## BIBLIOGRAPHY

## PREVALENCE OF HEART DISEASE AND OF THE ETIOLOGIC TYPES

- Arenberg H Heart Disease Among Seamen *Am Heart J* 1937 XIII 197
- Baunton J H Levy R L Munly W C and Pardec H E B (appointed by the Heart Committee of the New York Tuberculosis and Health Association Inc) *Criteria for the Classification and Diagnosis of Heart Disease* Paul H Hoeber Inc New York 4th ed 1943 (1st ed 1928)
- Cabot R C "The Four Common Types of Heart Disease An Analysis of Six Hundred Cases" *JAMA* 1914 LXIII 1461
- Case Records of the Massachusetts General Hospital Four Types of Heart Disease in One Case *New England J Med* 1941 CCXXIV 1108
- Chavez I "The Incidence of Heart Disease in Mexico" *Am Heart J* 1942 XXIV 88
- Clawson B J "The Incidence of Types of Heart Disease Among 30 265 Autopsies with Special Reference to Age and Sex" *Am Heart J* 1941 XXII 607
- Coffin T H "The Incidence of Heart Disease in the Pacific Northwest" *Am Heart J* 1929 V 99
- Cohn A E Statistical Studies Bearing on Problems in the Classification of Heart Diseases I Introduction *Am Heart J* 1926 I 442
- "An Analysis of the Apparent Increase in the Heart Diseases" *JAMA* 1935 CV 1394
- Cole L R Cardiac Disease Among 28 139 Newly Entering Students at University of Wisconsin *Am J M Sc* 1941 CCI 197
- Condry R J Heart Disease in West Virginia *West Virginia M J* 1932 XXVIII 485
- Coombs C F "The Aetiology of Cardiac Disease" *Bristol Med-Chir J* 1926 XLIII 1
- Cossio P "Heart Disease in the Argentine" *Am Heart J* 1943 XXV 145
- DePorte J V Heart Disease in General Medical Practice Preliminary Report of Morbidity Survey Conducted by the New York State Department of Health *Am Heart J* 1933 VIII 476
- Dublin L I Statistical Aspects of the Problem of Organic Heart Disease *Am Heart J* 1926 I 359
- Dublin L I and Marks H H A Note on the Inheritance of Cardiovascular Disease—Result of Insurance Investigations *J Mt Sinai Hosp* 1942 VIII 482
- Durbin E Heart Disease in Colorado *Rocky Mountain M J* 1939 XXVI 173
- Emerson H "The Prevention of Heart Disease—a New Practical Problem" The Shattuck Lecture *Boston M and S J* 1921 CLXXIV 587
- Fahback H R An Analysis of Coroners Statistics from Cook County (Chicago) Illinois With a Pathologic Review of the Causes of Death *Arch Path* 1934 XVII 775
- Flaxman N Heart Disease in the Middle West Incidence and Etiology of One Thousand Six Hundred and Forty six Cases at the Cook County Hospital *Am J M Sc* 1934 CLXXXVIII 639
- Gager L T and Dunn W L "Heart Disease in Washington D C Study of Etiologic Types and Factors of Race Age and Sex in One Thousand Two Hundred Cases" *M Ann District Columbia* 1933 II 112
- Geiger J C Sampson J J Miller R C and Gray J P "A Survey of Heart Disease Morbidity in San Francisco" *Am Heart J* 1936 XII 137
- Goodman M and Prescott J W Heart Disease Among Adolescent School Children of New York City *JAMA* 1934 CIII 157
- Grant R T After Histories for Ten Years of a Thousand Men Suffering from Heart Disease A Study in Prognosis *Heart* 1933 XVI 275
- Gunewardene H O *Heart Disease in the Tropics* Butterworth and Co., Ltd Calcutta 1935
- Hartwell A W and Lam J W "Heart Disease in Hawaii Review of 160 Consecutive Cardiac Cases seen in General Medical Clinic in Honolulu." *Hawai M J* 1943 III 71

- Hedley O F "Study of Four Hundred and Fifty Fatal Cases of Heart Disease Occurring in Washington (D C) Hospitals During 1932 with Especial Reference to Etiology Race and Sex" *U.S. Pub Health Rep* 1935 L 1127
- Trends Geographical and Racial Distribution of Mortality from Heart Disease Among Persons 5-24 Years of Age in the United States During Recent Years (1921-1976) *Ibid* 1939 LIV 2271
- Heimann H L Strachan A M and Heyman S C Cardiac Disease Among South African Non Europeans Preliminary Note *Brit M J* 1929 I 344
- King R L Heart Disease in the Pacific Northwest An Analytical Study of Mortality and Morbidity with an Analysis of Five Hundred and Fifty six Private Cases. *Northwest Med* 1935 XXIV 154
- Laws C L The Etiology of Heart Disease in Whites and Negroes in Tennessee *Am Heart J* 1933 VIII 608
- Mackenzie J *Diseases of the Heart* Henry Frowde Hodder and Stoughton Oxford University Press 3rd ed 1913 (1st ed 1908)
- Maher C C Sittler W W and Elliott R A Heart Disease in the Chicago Area A Study of the Etiological Factors in One Thousand Cases *JAMA* 1935 CV 763
- Metropolitan Life Insurance Co How Stable Is Our Death Rate? *Statistical Bull* 1938 XIX 6
- Myers M M The Symptoms of Heart Disease A General Discussion of Pain and Palpitation and a Report of a Study of 1000 Consecutive Patients *J Iowa State M Soc* 1927 XVII 388
- Ormhaug T Om hjertesygdommenes aarsaker ( Causes of Heart Disease ) *Norsk mag f laegevid* 1921 LXXII 868
- Parson G W Analysis of 500 Cases of Organic Heart Disease Etiologic Types and Their Incidence" *Texas State J Med* 1941 XXXVII 518
- Rathe H W and Paul W D Study of Incidence of Various Etiologic Types of Heart Disease in Iowa Review of One Thousand Three Hundred and Twenty Nine Cases *Iowa State J Med* 1933 XXIII 125
- Rauh L W The Incidence of Organic Heart Disease in School Children *Am Heart J* 1939 XVIII 705
- Robey W H (representing New England Heart Association) "A Cardiac Survey of Children in Boston Public Schools *The Nation's Health* 1927 IX No 17 p 71
- Rowntree L G McGill K H and Edwards T I "Causes of Rejection and the Incidence of Defects Among 18 and 19 Year Old Selective Service Registrants *JAMA* 1943 CXXIII 181
- Salcedo Sa'gar J Clinical Analysis of 522 Private Cardiovascular Cases in Bogota Colombia *Proc Eighth Annual Pan American Scientific Congress* Washington DC May 16 1940 Dept State 1942 p 161
- Sampson J J Christie A and Geiger J C Incidence and Type of Heart Disease in San Francisco School Children *Am Heart J* 1938 XV 661
- Schwab E H and Schulze V E The Incidence of Heart Disease and of the Etiological Types in a Southern Dispensary *Am Heart J* 1931 VII 273
- "Heart Disease in the American Negro of the South *Am Heart J* 1932 VII 710
- Scott R W and Garvin C F Incidence of Types of Heart Disease Among 6548 Autopsies with Observations on Race and Sex Presented before Am Heart Ass. Cleveland 1941
- Stone C T and Vanzant F R Heart Disease as Seen in a Southern Clinic A Clinical and Pathological Survey *JAMA* 1927 LXXXIX 1471
- Viko L E Heart Disease in the Rocky Mountain Region *Am Heart J* 1930 VI 264
- White P D and Jones T D "Heart Disease and Disorders in New England" *Am Heart J* 1928 III 307
- White P D and Myers M M "The Classification of Cardiac Diagnosis" *JAMA* 1921 LXXVII 1414
- Whitney J S *Heart Disease Mortality Statistics* (U.S. Registration Area) Am Heart Ass. New York 1927
- Wood J E Jr Jones T D and Kimbrough R D The Etiology of Heart Disease Clinical Study of 673 Cases with Certain Observations on Race and Climate" *Am J M Sc* 1926 CLXXII 185

Wycliff J and Lingg C "II Etiology in Organic Heart Disease" *Am Heart J* 1926 I 446

*Recent References (1944-1950)*

- Berk M E and Hartwell A S Five Years of Heart Disease in Hawaii *Hawaii M J* 1949 VIII 177
- Blanc G and Blomquist N "Studier over hjartkarlsjukdomarnas samhällliga betydelse i Sverige Den svenska befolkningens dödlighet i cardiovasculara sjukdomar under åren 1911-1945" *Social Med Tidskrift* Stockholm 1949 XXVI 215 and 243
- Collins S D Statistical Studies of Heart Disease V Illness from Heart and Other Cardiovascular renal Diseases in General Morbidity Surveys of Families *Pub Health Rep* 1949 LXIV 1439
- Dublin L I Metropolitan Life Insurance Company *Statistical Bill* 1949 XXX No 10 1950 XXXI No 1 and No 3
- Fenn G K Kerr W J Levy R L Stroud W D and White P II "Re-examination of 4994 Men Rejected for General Military Service Because of the Diagnosis of Cardiovascular Defects" *Am Heart J* 1944 XXVII 435
- Gage R P Statistics and Medicine The Need for Close Cooperation Between the Physician and Statistician in Medical Statistics" *Proc Staff Meet Mayo Clin* 1946 XXI 130
- Garcia Carrillo E "Some Cardiological Problems of the Tropics" *Am J M Sc* 1949 CCXVII 619
- Gover M Statistical Studies of Heart Diseases III Heart Disease Associated with Other Major Causes of Death as Primary or Contributory Cause *US Pub Health Rep* 1949 LXIV 104
- IV Mortality from Heart Disease (All Forms) Related to Geographic Section and Size of City" *Ibid* 1949 LXIV 439
- Gover M and Pennell M Y Statistical Studies of Heart Disease *US Pub Health Rep* 1950 LXV 819
- Hamilton B II Report from the Cardiac Clinic of the Boston Lying In Hospital for the First Twenty five Years" *Am Heart J* 1947 XXXIII 663
- Holoubek J E Holoubek A B and Baker D T Heart Disease in Charity Hospital of Louisiana in New Orleans A Survey of 8313 Routine Autopsies *New Orleans M & S J* 1947 XCIX 431
- Juca A Causas Das Cardiopatias No Ceara *Med Cirurgia Farmacia* 1948 CLI
- Landulfo J LeVoci I D Mascarenhas A and Spanghero C "Frequencia etiologica de cardiopatias na Cidade de Sao Paulo Revisao de estatisticas anteriores e estudo atual correlato na classe dos comerciantes" *Arg brasil de cardiol* 1949 II 297
- Lenègre J and Kilaionis P Étude statistique de 500 autopsies de sujets morts d'une hypertension arterielle ou d'une affection cardiaque dans des services hospitaliers parisiens" *Sem d Hop de Paris* 1949 XXV 3115
- Metropolitan Life Insurance Company "A Century of Progress in Longevity" *Statistical Bull* 1949 XXX No 10
- Health and Longevity at the Mid Century" *Ibid* 1950 XXXI No 1
- International Variation in Longevity *Ibid* 1950 XXXI No 3
- Mortiz A R Unexpected Death of Apparently Healthy Adults from Natural Causes *Northwest Med* 1948 XLVII 500
- Murgel L Contribuicao estatistica a etiologia das cardiopatias no Rio de Janeiro *Bo il M dico Cirurgico* 1948 X 163
- Ortiz Vazquez J "Incidencia de los diversos tipos de cardiopatias entre tres mil autopsias hospitalarias consecutivas" *Revista Espanola de Cardiol* 1950 IV 166
- Ortiz Vazquez J Duque A Perez Gonzalez P and Calderon Montero J Etiologia de las cardiopatias en Madrid Un analisis de mil casos consecutivos" *Revista Espanola de Cardiol* 1949 III 331
- Porter R R "Cardiovascular Experiences in an Army General Hospital" *Am Heart J* 1944 XXVII 559
- Ramos J Le Vocci I Ratio O Gorges S and Lindenberg S Frequencia etiologica das cardiopatias em Sao Paulo (Brasil)" *Arg brasil de cardiol* 1949 II 181
- Robinson S J Aggeler D M and Dansloff G T Heart Disease in San Francisco

- School Children 1947 Registry Showing Incidence Problems and Supervision Techniques *J Pediatr* 1948 XXXIII 49
- Suárez R M 'The Incidence of Heart Disease in Puerto Rico' *Am Heart J* 1945 XXIX 339
- Tecce N and Lombardi A Sulla reale incidenza delle malattie cardiovascolari tra le cause di morte *La Riforma Medica* 1949 LXIII 833
- Tranchesí II Cavalheiro Dias J Nussenzeig I Tisi O G Tranchesí J and Fabio Lion M A etiologia das cardiopatias em São Paulo (Brasil) *Arq brasil de cardiol* 1951 IV 31
- Traum A H and Wilcox B II Cardiovascular Disease Among Veterans of World War II *New England J Med* 1946 CCXXXIV 82
- Vakil R J A Study of Rheumatic Heart Disease in Bombay Province (India) (From a total medical inpatient population of 30 104 patients) *Indian Heart J* 1949 I, 15
- Wartman W B and Hellerstein H K The Incidence of Heart Disease in 1,000 Consecutive Autopsies *Ann Int Med* 1948 XXVIII 41
- Welch O and Porter C Heart Disease in Alabama *Alabama State M A J* 1948 XVII 213
- Woolsey T D and Moriyama I M Statistical Studies of Heart Diseases II Factors in Trends of Heart Disease Mortality *Pub Health Rep* 1948 LXIII 1747

---

## CHAPTER 13

---

### CONGENITAL CARDIOVASCULAR DEFECTS

---

**Introduction** Congenital defects of the heart and blood vessels though not frequent comprise one of the most difficult important and interesting medical problems of our day. More progress has been made in our understanding of their clinical significance and in their recognition during the last two decades than in any other type of heart disease. The successive editions of this book which were begun just twenty years ago illustrate this well. Also considerable and spectacular advances have been made in the surgical correction and amelioration of several of these defects and intracardiac catheterization has been applied especially in this field. Table 5 (page 294) presents in summary the current clinical status of the congenital defects of the heart and great vessels. Less important extremely rare or as yet undiagnosable defects are not included in this table but are for the most part mentioned in the listing of 1 000 autopsied cases collected and classified by Maude Abbott. Because of its historic interest and value pathologically her classification and figures have been retained in this edition but the tabulated insert has been omitted.

Mention need be made herewith only of two rare anomalies incompatible with life namely acardia (absence of heart) and hemicardia (absence of half the heart) these conditions were reported by Maude Abbott in 15 cases of an early series of hers of 850 autopsied cases (1928).

**Incidence** We still await adequate statistical information about the absolute and relative incidence of congenital cardiovascular disease in various parts of the world. Our current impression is that it is found everywhere and in about the same total incidence but that it varies a good deal relatively depending on how much heart disease there is in general and so far as children are concerned on how much rheumatic heart disease there is in any district or community. Statistics already available but as a rule still crude indicate a low total incidence averaging well under 1 per cent of all deaths. An analysis of 34 023 unselected autopsies in Boston showed congenital cardiovascular disease in 1.33 per cent but this figure dropped to 0.5 per cent after the age of two (Gelfman and Levine 1942). An incidence of 0.9 per cent of con-

genital heart disease among 15 597 autopsies was reported by Clawson (1944) of this lot of 141 infants 18 were stillbirths and 83 died in the first five months of life only 30 cases (21·3 per cent) surviving after their first year. A clinical series of 31 771 medical outpatients in Copenhagen contained 85 cases (0·27 per cent) diagnosed as congenital heart disease among 4 746 individuals with cardiovascular abnormalities (a relative incidence of 1·8 per cent) (Thordarson 1947). In a clinical series of cardiac patients under the age of twenty years in New England 6 per cent were found to be of congenital origin (White and Jones 1928) this figure would doubtless have been higher had more young infants been included since many of those severely involved die very young. In California some years ago (1936) it was noted that the ratio of congenital to rheumatic heart disease was very different from that in New England being very much greater recent statistical information confirms the earlier figures among San Francisco school children there being 0·19 per cent with congenital heart disease and 0·24 per cent with rheumatic heart disease a ratio of about four to five while the ratio in New England was once about one to ten until recent years when with the decrease of rheumatic heart disease and the increase of congenital cardiovascular cases seeking help the ratio has changed in New England to about two congenital to three rheumatic (actually 165 of the former and 257 of the latter under the age of twenty years among 2 000 cardiac patients—White 1951).

**Etiology Cause** One of the three great advances in our knowledge of this kind of heart disease during the past decade not known when the third edition of this book was being prepared has been the first clear evidence of a causative factor the other two advances being more accurate diagnosis and surgical treatment respectively. In the last edition certain guesses were mentioned including alcoholism syphilis trauma fetal endocarditis and defects in the germ plasm but there was no clear knowledge. It is still quite possible that some of these factors and others not mentioned or even thought of may prove eventually to play a role but the one substantiated factor discovered in Australia a few years ago (Gregg 1941 Swan 1943) was not mentioned earlier. This is German measles (rubella) a virus disease, which appears to result in a combination of congenital defects (cataracts cardiovascular anomalies and at times deaf mutism and mental maldevelopment) in a considerable percentage of instances in which the mother is affected during the first two to three months of pregnancy. The exact percentage is not yet known but has been to date estimated to be from one quarter to one half of the cases or even more. One of the most recent reports (Wesselhoeft 1949) cites 67 infants with congenital heart lesions born of 132 mothers who had had rubella during the first trimester of pregnancy. More recently other viruses have been suspected of causing congenital defects of heart and aorta in the fetus during early pregnancy but accurate information about this is still lacking.

Our newly acquired knowledge about rubella and congenital heart disease gives us our first real hope about preventative measures. At present the first crude steps have been taken in the way of advice to terminate pregnancy if rubella occurs during the first trimester or to attempt to infect girls and

young women before marriage but of course the vital need ■ early cure and prevention of the viruses themselves. Gamma globulin has been suggested but its value has not been substantiated as yet in the case of rubella.

Not rarely the apparent scarring with fibrosis and contraction of the endocardium ■ the right ventricle involving especially the infundibular area and the pulmonary valve itself strongly suggests the possibility of fetal endocarditis. If this should be proved to be true we may again have weapons against such involvement in the form of modern chemotherapy and penicillin and its like. In fact it will be of interest to determine whether in the future there may be a decrease in the incidence of infundibular and pulmonary stenosis associated with the current extensive use of these new therapeutic agents during pregnancy. On the other hand the white fibrotic thickening of the endocardium per se as in the case of congenital anomalies of the coronary arterial circulation (in particular when the left coronary artery arises from the pulmonary artery) is ascribed best to the effect of prolonged anoxia.

**Sex** There ■ a curious relationship of sex in certain congenital cardiovascular defects. In the largest series of cases on record (1 000 cases with the sex stated in 859 Abbott 1931) the ratio of males to females was 58 to 42. It happened that in some of the individual lesions of this series the sexes were about evenly divided but pericardial defects (21 males to 9 females) cor biloculare i.e. two chambered heart and triloculare i.e. three-chambered heart (17 to 10) defects of aortic septum (28 to 11) transposition of arterial trunks (42 to 18) anomalies of the semilunar valve cusps (32 to 5) and coarctation of the aorta (60 to 19) were much commoner in the male while simple patency of the ductus arteriosus was more common in the female (55 to 29) and in the 53 cases of true atrial septal defect studied by Bedford Papp and Parkinson (1941) there was a female preponderance of 4 to 1. More cases however are needed to allow one to be at all certain of these proportions. Recently the large series of cases of ductus patency operated upon by Gross (personal communication January 1950) gives a ratio of 276 females to 120 males and of coarctation of the aorta by Reifenshtein et al (1947) gives one of five males to one female.

**Age** Congenital heart disease may be found at any age but it is commonest of course in the infant and young child because many of the victims survive but a few years at the most and often only a few days or months. The diagnosis ■ much more difficult however in very young children than at an older age because of the absence or paucity of symptoms and signs. This explains why the percentage of accurate clinical diagnoses can be and often is higher in general hospitals than in children's or infants' hospitals. The age to which the patient lives depends largely on the degree of cyanosis and on the size of the heart. Markedly cyanosed children and those with very large hearts rarely survive to adolescence or to full adult age or at most beyond 30 years. Delay in closure of a ductus arteriosus or of a foramen ovale during the first few months of life should not be interpreted as abnormal.

**Race** Congenital cardiac defects have been reported in every civilized race they do not seek any particular country or climate.



*Social status* Favorable social status and financial resources have not yet been shown to prevent congenital heart disease but they do favor longevity

*Pathology* The individual defects found in congenital heart disease will be discussed later in this chapter. The most common defects in Abbott's post mortem series of 1 000 cases are interatrial septal defects (373 cases) inter ventricular septal defects (274 cases) simple patency of the ductus arteriosus (242 cases) pulmonary stenosis (151 cases), anomalies of the cusps of the semilunar valves (146 cases) coarctation of the aorta (adult type) (105 cases) anomalies of the great veins (94 cases), and complete transposition of the arterial trunks (74 cases)

Cases with combined cardiovascular defects are more common than those with the individual defects alone. This is particularly true of interatrial septal defects, pulmonary stenosis, interventricular septal defects, and patency of the ductus arteriosus. In Abbott's series of 1 000 cases mentioned above, an atrial septal defect was noted as the primary lesion in but 73 cases, while it complicated other lesions in 300 cases; interventricular septal defects were classified as the primary lesion in 55 cases and as a complication of other lesions in 219 cases; simple patency of the ductus arteriosus occurred primarily in 92 patients and as a complication in 150 others, and pulmonary stenosis occurred alone in but 9 cases, while it was combined with other defects in 142 cases. As a matter of fact it is to be expected that the defects should be complicated either through the simultaneous involvement of several areas of the heart in the embryonic maldevelopment or through the pressure effects secondarily resulting from a single lesion, like pulmonary stenosis, aortic stenosis, or in *cuspid atresia* (complete closure) to keep patent the ductus arteriosus and defects in the septa between atria and between ventricles. Only in certain instances, as in the case of pericardial defects, of primary congenital hypertrophy, and of coarctation of the aorta, do the defects tend to be isolated rather than in combination.

The stage in the development of the embryo at which retardation or abnormality of growth occurs determines largely the type of congenital heart disease found later. If the abnormality comes relatively early before the septa have appeared or have grown appreciably, the heart may remain, as in the case of the primitive vertebrate heart (that of the fish), with but one atrium and one ventricle (*cor biloculare*); if the defect in growth begins later, the heart may be three chambered, as in the case of the reptile, with two atria and one ventricle (*cor triloculare biatriatum*). Much less commonly the three-chambered heart has two ventricles and one atrium (*cor triloculare biventriculare*).<sup>1</sup> Later in the stage of embryonic growth after the septa have almost completely formed, a defect may cause a permanent opening in the interatrial septum (which may be either a patent foramen ovale or a persistent ostium) or an aperture at the base of the interventricular septum just anterior to the unde-

<sup>1</sup> A unique freak of nature has been reported by Sinclair (1944) of a five-chambered heart with two atria, a right ventricle, and two left ventricles in a two-headed human monster with two aortas and two pulmonary arteries.

fended space. Also at this stage or earlier the common truncus arteriosus may not be completely divided into aorta and pulmonary artery leaving so called partial or complete defects of the aortic septum. If in the course of growth of the embryo there is either (1) reversed torsion of the ventricular bend of the embryonic heart (2) malposition of the aortic septum in relation to the interventricular septum or (3) incomplete involution of the aortic part of the conus a transposition of the great vessels may result the aorta arising from the right ventricle and the pulmonary artery from the left.

In the explanation of transposition of the great vessels in particular Spitzer's important phylogenetic theory deserves a leading position (1923). Harris and Farber (1939) have written about it as follows:

Spitzer's main contribution is a theory of normal cardiac development. The fundamental postulate of that theory is the orderly development of the organ as a unit in response to the varying conditions, forces and demands in a series rising from fishes to birds and mammals. It admits of no fortuitous variations which disregard the phylogenetic interrelations of these groups.

With the advent of pulmonary respiration in phylogeny a very much greater volume of blood must pass through the heart. Bending alone becomes inadequate to compensate for the lengthening tendency and torsion must take place. The original right bend initiates the torsion to the right and the bulbar elements are thrown into a clockwise spiral. Since the heart is fixed at both ends detorsion must take place and a counter clockwise spiral must be present at the opposite or venous end.

"According to Spitzer this is the most important stage in cardiac development. Without it no advance could take place with faulty degrees of torsion the most bizarre anomalies result. The concept of torsion recurs repeatedly through Spitzer's hypothesis and its importance cannot be underestimated. The septum formation must not only separate the pulmonary and systemic circuits but also cross the circuits so that systemic venous blood enters the pulmonary artery and oxygenated blood passes out through the aorta. A straight septum could only cause the circuits to exist side by side as in cases of complete transposition. Torsion conditions the necessary spiral at the arterial end and thus permits the crossing over of the circuits. In order that the countertorsion may not undo this effect the countertorsion must take place peripheral to the entrance of the pulmonary veins. Furthermore it is through the torsion that the course of the longitudinal folds along which the blood flows easily is directed more or less into the current. The forces residing in the blood stream may then work on the folds stimulate them to grow and cause them to develop into septums.

A failure in development of the conus arteriosus or perhaps an infection involving it or its valve cusps after it has become differentiated into the infundibulum of the right ventricle results in pulmonary valve or oftener infundibular stenosis or atresia. If this stenotic defect comes late it may occur as the only ventricular abnormality but this rarely happens generally it develops early along with failure of the interventricular septum to close completely with diversion of the blood into the aorta from the right ventricle in

■ variable but usually considerable degree In most of such cases the aorta is dextroposed overriding in varying extent the ventricular septal defect and best explained by Spitzer's theory It ■ this combination of pulmonary stenosis interventricular septal defect dextroposition of the aorta and hypertrophy of the right ventricle that is more commonly found than any other cardiac condition in children (over a year old) and adults with cyanosis resulting from congenital heart disease This is the so called tetralogy of Fallot described by Stensen (Steno) in 1672 Sandifort in 1777 Hunter in 1784 Farre in 1814 Gintrac in 1824 and Peacock in 1858 but analyzed more completely as a clinical entity by Fallot in 1888

Fallot A Contribution a l'anatomie pathologique de la maladie bleue (cyanose cardiaque) *Marseille med* 1888 XXV 77 138 207 270 341 and 403

Fallot's conclusions are as follows (translation by myself)

1 Clinicians have until now considered the precise diagnosis of the anatomic lesions of congenital heart disease with cyanosis (la maladie bleue) as almost impossible and to be expressed in the form of an entirely vague and uncertain hypothesis From observations that we have assembled it appears on the contrary that congenital heart disease with cyanosis above all in adults is the result of a small number of perfectly definite cardiac malformations

2 Of these malformations there is one which in frequency surpasses all others since we have met it in almost 74 per cent of our observations it is this malformation then that the clinician will be justified in diagnosing and in so doing the chances of error which he will run will be relatively few

3 This malformation constitutes a true pathologic anatomic type represented by the following tetralogy (1) stenosis of the pulmonary artery (2) interventricular septal defect (3) deviation of the origin of the aorta to the right and (4) hypertrophy of the right ventricle almost always concentric in type At times there ■ an additional entirely accessory defect namely patency of the foramen ovale

4 One cannot at the present time attribute the maladie bleue to the persistence of the foramen ovale without direct opposition to the great majority of observed facts when the communication between the two auricles exists alone without any other associated cardiac lesion cyanosis does not result

5 From the historical point of view one finds in the writings of the last century (the eighteenth) and of the beginning of the present frequent observations of congenital heart disease with cyanosis the majority present the interesting combination of the various cardiac lesions mentioned above

6 Finally from the pathogenic point of view the theory that considers the interventricular communication as a simple phenomenon belonging to the group of recessive anomalies rests only on a superficial and inexact interpretation of the facts the incompletely developed septum in the victim of the maladie bleue can be considered in no way as the analogue of the false septum of vertebrate animals with communicating ventricles it appears much more logical and more in keeping with physiological laws to regard the entire series of cardiac anomalies enumerated above as the consequence of the stenosis of the pulmonary artery As to the cause of this pulmonary stenosis we believe that we should attribute it not to a simple arrest in development but rather to a pathological process occurring in the region

of the pulmonary valve and of the infundibulum just below it during intrauterine life"

Much rarer than the tetralogy of Fallot ■ another somewhat similar combination of congenital defects consisting of dextroposition of the aorta (which is quite likely the primary condition as indeed it may be also in the tetralogy of Fallot) interventricular septal defect large right ventricle and normal or increased size rather than stenosis of the infundibulum and pulmonary valve and artery (Eisenmenger 1897 Rosedale 1935) A new entity associated with persistent cyanosis from birth with clinical fluoroscopic and electrocardiographic findings very similar to Eisenmenger's complex with which it is likely to be confused has been recently described by Taussig and Bing (1949) This new entity includes transposition of the aorta and a partial overriding of a ventricular septal defect by the large pulmonary artery arising primarily from the right ventricle

Finally of the commoner defects coarctation of the aorta and permanent patency of the ductus arteriosus appear latest of all at birth or shortly after when the heart and great vessels have otherwise attained normal growth and relations they may then occur alone probably because they are late defects Patency of the ductus arteriosus may really be designated as a postnatal defect since normally the ductus does not close until the first few days weeks or months after birth the ductus arteriosus was closed before the age of ■ weeks ■ 88 per cent of 558 normal infants hearts and the foramen ovale prior to 12 weeks after birth in 87 per cent of this same group (Christie 1930) Recently Everett (personal communication 1951) has found that the foramen ovale closes sooner after birth considerably before the ductus arteriosus

**Clinical classification of congenital cardiovascular disease** Various attempts have been made to group the different congenital cardiac defects and their combinations in order to produce a useful clinical classification not following necessarily any embryologic or pathologic plan A classical arrangement is that of the division of the cases into three groups (Abbott 1924 1928 1936) this arrangement is shown slightly modified in details in the following plan It may be said that the greater the degree of cyanosis the more serious is the case

Table 4

# CLASSIFICATION OF CONGENITAL CARDIOVASCULAR DISEASE (ABBOTT)

(Order based on degrees of oxygen unsaturation and duration of life in 1 000 autopsied cases analyzed by Abbott )

1 Cases without Abnormal Communications or Shunts between the Right and Left Sides of the Heart Acyanotic Group The lesions of these cases cause varying degrees of cardiac strain from little or none to a great deal Here belong the following relatively unimportant defects as well as more important anomalies

## A. Less important group

1 Simple dextrocardia usually with the situs inversus No limitation of life unless there are other congenital cardiovascular defects

2 Anomalies of the pericardium Defects and diverticula Maximum age = 75 years mean age at death in 36 cases = 45 years

3 Anomalous chordae Maximum age = 84 years mean age in 23 cases = 43 years

4 Uncomplicated quadricuspid and bicuspid semilunar valves more often aortic than pulmonary bicuspid aortic valves are a frequent site for bacterial endocarditis and so cannot be considered to be wholly unimportant Maximum age = 80 years mean age in 44 cases = 34 years

5 Double atrioventricular orifices Maximum age = 71 years mean age in 9 cases = 37 years

6 Pure coarctation of the aorta of adult type Maximum age = 92 years mean age in 70 cases = 33 years

7 Anomalies of aorta (such as right aortic arch) of the aortic branches of the coronary arteries of the pulmonary arteries and of the great veins unless these are extreme Very variable duration of life but as high as 87 years with double aortic arch (and as low as 3 months with left coronary artery arising from the pulmonary artery)

#### B More serious group

1 Ectopia cordis (extrathoracic heart in the abdomen) extra abdominal ectopia cordis does not allow survival for more than a few days Maximum age = 15 months mean age in 7 cases = 1 month

2 Primary congenital hypertrophy of the heart Maximum age = 4 years mean age in 15 cases = 10 months

3 Pure subaortic or aortic stenosis which exerts a considerable strain on the left ventricle Maximum age = 58 years mean age in 23 cases = 13 years

4 Pure mitral stenosis very rare Maximum age = 27 years mean age in 6 cases = 5½ years

5 Pure coarctation of the aorta of infantile type maximum age = 9 months mean age in 9 cases = 1¾ months

II *Cases of Arteriovenous Shunt with Possible Terminal or Transient Reversal of Flow (Cyanose Tardive)* In these cases arterial blood ordinarily enters the pulmonary circulation while venous blood rarely enters the systemic circulation Potentially cyanotic group

1 Patent ductus arteriosus Maximum age = 66 years mean age in 92 cases = 24 years

2 Localized defects of aortic septum (communication between base of aorta and pulmonary artery or base of right ventricle) Maximum age = 48 years mean age in 10 cases = 14 years

3 Localized defects of the interatrial septum including widely patent foramen ovale persistent ostium primum and persistent ostium secundum Maximum age = 70 years mean age in 68 cases = 27 years

4 Localized defects of the interventricular septum *Maladie de Roger* (Roger 1879) Maximum age = 49 years mean age in 50 cases = 14½ years

III *Cases of Venoarterial Shunt (Morbus caeruleus) (Maladie bleue)* Hem venous blood in considerable quantity enters the systemic circulation Cyanotic group

## A. Slight to moderate cyanosis

- 1 Defect of interventricular septum with dextroposition of the aorta Maximum age = 48 years mean age in 7 cases = 25 years
- 2 Cor triloculare biatrnatum. Maximum age = 35 years mean age in 13 cases = 7½ years
- 3 Pulmonary stenosis with patent foramen ovale Maximum age = 57 years mean age in 16 cases = 18 years
- 4 Tricuspid stenosis Maximum age = 28 years mean age in 3 cases = 15 years
- 5 Tricuspid atresia (imperforation from α privative not and τρυσις perforation) with septal defects Maximum age = 56 years mean age in 16 cases = 5 years

## B. Moderate to marked cyanosis

- 1 Pulmonary stenosis with defect of ventricular septum and dextroposition of aorta (tetralogy of Fallot 1888 the fourth element of the tetralogy being right ventricular hypertrophy) Maximum age = 59 years 8 months mean age in 85 cases = 12 years
- 2 Pulmonary atresia with defect of ventricular septum and dextroposition of the aorta Maximum age = 30 years mean age in 30 cases = 5 years
- 3 Transposition of arterial trunks with defect of ventricular septum Maximum age = 16 years mean age in 17 cases = 2½ years

## C. Extreme cyanosis

- 1 Cor biloculare with transposition of arterial trunks Maximum age = 16 years mean age in 2 cases = 9 years
- 2 Persistent truncus arteriosus (complete defect of aortic septum) with localized defect of interventricular septum Maximum age = 25 years mean age in 21 cases = 4 years
- 3 Cor biloculare with persistent truncus arteriosus (complete defect of cardiac and arterial septa) Maximum age = 14 days mean age in 5 cases = 6½ days
- 4 Complete transposition of arterial trunks without defect of ventricular septum but with interatrial septal defect or patency of the ductus arteriosus Maximum age = 11 years mean age in 32 cases = 6 months
- 5 Pulmonary atresia with closed ventricular septum defective atrial septum and patent ductus arteriosus Maximum age = 20 years mean age in 10 cases = 1½ years
- 6 Mitral atresia with aortic aplasia (lack of development from α privative not and πλασσειν to form) defect of atrial and ventricular septa and patent ductus arteriosus Maximum age = 3½ years mean age in 5 cases = 10 months
- 7 Aortic atresia transposition of arterial trunks closed ventricular septum patent ductus arteriosus Maximum age = 15 weeks mean age in 12 cases = 2 months

A practical clinical classification which the author has recently found very helpful is presented in Table 5

Symptoms Congenital heart disease may be present without any symptoms whatsoever if there is no venoarterial shunt or especial strain on the heart such as commonly the case when there is but a slight to moderate degree of

DIAGNOSABLE CONGENITAL DEFECTS OF HEART AND GREAT VESSELS—1990

\*Tricuspid regurgitation is a common finding in patients with congenital heart block and cor tri-auriculatum (both very rare) may be diagnosed by electrocardiogram.

Table 5—Continued

## DIAGNOSABLE CONGENITAL DEFECTS OF HEART AND GREAT VESSELS—1950

TYPE	ECG	BLOOD	CARDIAC CATHETERIZATION	SURGICAL RELIEF
Normal	\ normal or left ventricular hypertrophy	\ normal	\ normal	0
Pulmonary artery now enlarged pulmonary artery arteries usually decreased	Right ventricular hypertrophy ++	\ normal	Pulmonary artery pressure less than pulmonary artery pressure	\ normal
Very large pulmonary artery of heart dilation. Heart lightly enlarged	R \ H ++	\ normal	Increased pressure in right ventricle Increased pulmonary artery pressure	Begin test
\ normal right heart left heart defects left heart in 2 b enlarged	L small \ normal	\ normal	Increased pressure in right ventricle	Declining
Coronary artery with pulmonary artery dilation. Pulmonary artery with left ventricular artery decreased	R \ H ++	Pulmonary artery decreased blood flow	Coronary artery pressure pulmonary artery pressure decreased pulmonary blood pressure	Partial relief (bypass)
Much as in the case of the coronary artery dilation	R \ H ++	Pulmonary artery decreased blood flow	The coronary artery pressure is lower than the pulmonary artery pressure. In the case of Tetralogy of Fallot the coronary artery pressure is increased	Probably valvular
\ normal or pulmonary artery right ventricle	R \ H +	Normal	Coronary artery pressure pulmonary artery pressure decreased	0
Small left ventricle and pulmonary artery	L \ H	Normal	Coronary artery pressure pulmonary artery pressure decreased	Partial relief (bypass)
Both ventricles in enlarged. Correlation of heart with left ventricle and right ventricle	R \ H L small	Normal	Coronary artery pressure pulmonary artery pressure decreased	0 (bypass) + left ventricle septal defect
Large right ventricle normal pulmonary pulmonary artery	R \ H +	Normal	Coronary artery pressure pulmonary artery pressure decreased	On trial (bypass) + left ventricle septal defect
Small aortic dilation	\ normal hypertension in thorax	\ normal	\ normal	+
Small pulmonary pulmonary	\ normal	\ normal	Increased pressure in pulmonary artery pulmonary pressure	+
Coronary artery pulmonary artery dilation	\ normal	\ normal	\ normal	+



uncomplicated patency of the ductus arteriosus coarctation of the aorta, or pure interventricular or interatrial septal defect. On the other hand there may be marked symptoms if serious congenital cardiovascular lesions are present especially those attended by marked or extreme cyanosis (Groups III B and III C of Abbott's classification) and those with primary congenital hypertrophy marked coarctation of the aorta or pure stenosis of any of the valves.

The symptom most commonly found is dyspnea particularly on exertion. This dyspnea is of all grades occurring in the case of atrial septal defects as the result of overloading the pulmonary circulation and thus leaving too little room in the lungs for air and in the morbus caeruleus in paroxysms due probably to temporary increase of the amount of venous blood shunted into the systemic circulation which leads in turn to the appearance or increase of cyanosis. Often there is but little dyspnea hardly noticeable which may show itself simply as an increase in respiratory rate. Dyspnea was noted in 320 of Abbott's series of 1 000 cases of congenital heart disease.

An interesting symptom doubtless related to both dyspnea and weakness is the frequent squatting during short walks or other exercise characteristic of children with the morbus caeruleus commonly the tetralogy of Fallot.

Along with the higher grades of dyspnea cough is common hemoptysis is rare but may occur if there is pulmonary vascular engorgement from obstruction polycythemic congestion or heart failure. Polycythemia may also give rise on occasion to epistaxis.

Next in frequency after the respiratory and pulmonary symptoms are those of cerebral nature due chiefly to anoxemia but in the case of considerable polycythemia they are also due to the sluggish circulation and to cerebral thrombosis. Weakness faintness headache dizziness syncope convulsions and coma delirium mania and transient or persistent paralyses have all been noted particularly in the cyanotic group of cases with congenital heart disease. The greater the degree of cyanosis the greater is the likelihood of such cerebral seizures. The cerebral manifestations may last from a few seconds to days at a time they often mean that the patient has been overtaking his reserve. In some cases they recur at intervals of a few days weeks or months for many years. Not rarely they are the cause of death in the cyanotic cases. Paradoxical cerebral embolism in cases with septal defects is responsible on occasion for abscesses of the brain.

Gastrointestinal symptoms in congenital heart disease are not important except for the dysphagia caused by some anomalies of the aorta and its branches especially a right aortic arch. Faulty circulation to the abdominal viscera may occasion anorexia nausea vomiting hematemesis tympanites constipation and combinations labeled biliousness. If congestive failure supervenes an increase of such symptoms is common due especially to engorgement of the liver.

Other symptoms are infrequent except for the complaint of coldness of hands and feet with cyanosis tingling in the extremities and abnormal susceptibility to infections especially of respiratory nature. Palpitation is some

times complained of it is rarely severe. Pain is very rare compared to dyspnea.

**Signs.** Often there are no signs of congenital heart defects outside of the heart and sometimes there are none even in the heart itself.

Of all general signs only one is both common and important and that is cyanosis found in slight to marked degree in less than half of the cases of congenital heart disease (noted in 475 cases of Abbott's series of 1 000 doubtless an exaggerated proportion because cyanotic cases attract much more attention than noncyanotic). It may be terminal only due either to a reversal of flow between the sides of the heart through a shunt or to congestive failure or to both. It was terminal in 124 of Abbott's series of 475 cyanotic cases. It is particularly likely to be delayed in appearing after birth but it may become very intense in late childhood and in adult life giving rise to the terms *morbus caeruleus* and *maladie bleue* (blue disease). In Chapter 4 cyanosis has already been discussed here it need only be reiterated that it is dependent on three factors: (1) the shunt of venous blood into the systemic circulation which shunt must be about 30 per cent of the total to pass the threshold for cyanosis; (2) the dilatation of skin and mucous membrane capillaries with peripheral slowing of the blood stream; and (3) insufficient oxygenation of the blood in the lungs. The first two of these three factors are commonly present in the cyanotic group of cases of congenital heart disease and sometimes the third factor is also added if there is engorgement of pulmonary blood vessels such as occurs in cases of atrial septal defects with overloading of the lesser circulation or if there is pulmonary arterial and arteriolar sclerosis due to pulmonary hyperemia or hypertension or with increased viscosity of the blood in polycythemia, or in the rare cases of failure of the left ventricle and of congenital mitral stenosis. A blueness of the eye grounds, cyanosis retinae may be a relatively early sign of the *morbus caeruleus*.

The next most characteristic and constant sign in the severe cases that is in those with well-marked and chronic cyanosis is clubbing of the fingers and toes (Figure 63). This was noted in 132 of Abbott's series of 1 000 cases. It varies greatly in degree as does cyanosis and like cyanosis is not frequent in the youngest infants or children; it develops later than cyanosis.

Malnutrition and faulty development are not necessary accompaniments of congenital heart disease even of the severer types but they have frequently been found. In Abbott's series delayed development was noted 150 times. Faulty cerebral growth, mental retardation and Mongolian idiocy have been occasionally associated with congenital heart disease. Arachnodactyly consisting of spider like fingers (and toes) and elongation of the entire body is seen in rare cases of congenital heart disease and hardly if ever occurs without cardiovascular defects, mostly atrial septal and aortic wall defects.

Edema of lungs and of legs, ascites and congestion of the liver occur in congenital heart disease only if congestive failure supervenes.

**Cardiac examination.** Physical examination of the heart yields signs dependent on the type and degree of the congenital defects. There may be little or no evidence of trouble in the heart even in some of the cases with such

serious lesions as the tetralogy of Fallot (pulmonary stenosis ventricular septal defect dextroposition of the aorta and big right ventricle) (Figure 64) There usually is but little enlargement in some cases however the apex impulse and the left border of dullness are well beyond the midclavicular line more increased transversely in the fifth intercostal space than downward in the sixth or seventh spaces since the right ventricle is enlarged more often than the left in congenital heart disease (Figure 71 opposite page 318) There may be increase in dullness to the right of the sternum usually there is not unless the heart shows well marked general enlargement or an abnormal position (dextrocardia) The region of the great vessels shows no abnormal dullness except with a patent ductus arteriosus or an atrial septal defect when the pulmonary artery may show itself to be enlarged by percussion in the

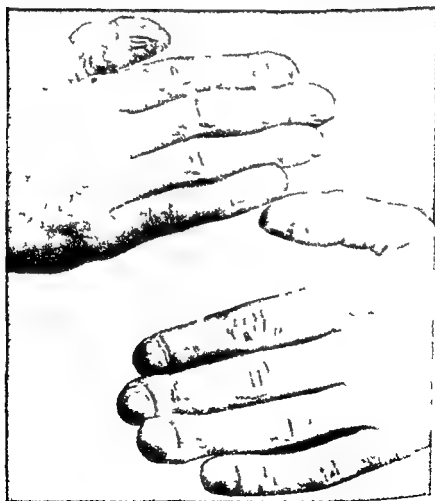


FIG 63 Photograph showing clubbing of the fingers in the morbus caeruleus (maladie bleue)

second and third intercostal spaces at the left of the sternum. Palpation usually reveals a more or less normal apex impulse. Occasionally there is felt a systolic thrill located at the left border of the sternum midway between upper and lower ends if there is a pure interventricular septal defect somewhat higher if there is pulmonary or infundibular stenosis and maximally in the second right intercostal space if there is congenital subaortic or aortic stenosis. There often is a continuous thrill at the left border of the upper sternum in cases of patent ductus arteriosus.

Auscultation may reveal no abnormalities even with serious congenital

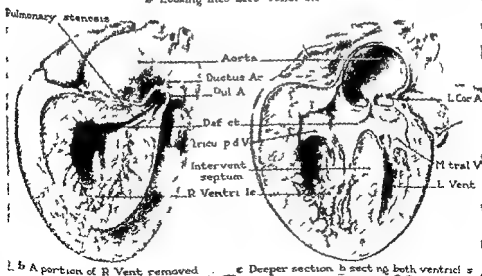
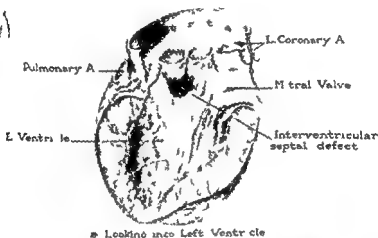


FIG 64 Photograph of congenital heart showing very large right ventricle in tetralogy of Fallot (Kindness of Dr Helen Taussig Johns Hopkins Hospital Baltimore and The Commonwealth Fund New York City)

defects There may or may not be murmurs When murmurs occur they are as a rule systolic in time and loudest just to the left of the sternum where they may be very limited in extent, located in the first intercostal space in some cases of patency of the ductus arteriosus, in the second space with pulmonary stenosis in the third space with infundibular stenosis and in the third and fourth interspaces in most cases of interventricular septal defect (Rogers murmur) Diastolic murmurs are uncommon as solitary findings they have been noted where the pulmonary or aortic valve has been defective and in rare cases of patency of the ductus arteriosus or larger interatrial septal defects They may also accompany the systolic murmurs of dilated pulmonary arteries in cases of large atrial septal defects when they are the result of a stretching of the pulmonary valve rings—such murmurs are likely to be transient like the Graham Steell murmur A continuous murmur roaring and machine like in character extending throughout systole and diastole with systolic accentuation is not infrequently found in the first three intercostal spaces just to the left of the sternum maximal in the first space When present it is usually pathognomonic of patency of the ductus arteriosus if venous hums transmitted from the neck and very rare and obvious arteriovenous aneurysms of the great vessels are excluded such exclusion is easily accomplished

It is important to remember that murmurs and thrills are very variable accompaniments of congenital heart defects the larger the defect the less likely are murmurs and thrills to be found A narrow caliber of patent ductus arteriosus or of interventricular septal defect is much more likely to give rise to murmur and thrill than is a large and much more serious patency which may show no murmur or thrill at all In the case of a stenotic lesion like pulmonary stenosis or coarctation of the aorta the greater the degree of stenosis the more frequently are murmur and thrill to be found but here too when the defect is extreme and there is complete atresia murmur and thrill will be absent One must use much judgment therefore in the analysis of the findings on physical examination of the heart in congenital cardiac disease it is necessary to depend more on other methods of examination

Heart sounds rate and rhythm are generally not abnormal in cases with congenital cardiovascular defects except in the case of pulmonary stenosis when the second sound in the second left interspace tends to be much diminished while with ductus patency or atrial septal defect it is usually accentuated With failure the sounds may decrease and the rate may increase but marked disturbances are rare and arrhythmia is very uncommon Premature beats and paroxysmal tachycardia are seen infrequently Atrial fibrillation is very unusual There is one disturbance of rhythm however which is an important though rare accompaniment of congenital heart disease this is heart block A few cases of unquestionable congenital heart block are on record The block may be either partial or complete It has been thought to be associated with interventricular septal defect and in three cases with postmortem study this defect was found to be extensive in degree (Wilson and Grant 1926 Yater 1928 and personal communication Abbott 1930)

**Blood pressure** The systolic blood pressure in congenital heart disease is not remarkable. It tends to be low especially where there is an atrial septal defect or subaortic (or aortic) stenosis or much polycythemia and peripheral vasodilatation then the pulse pressure also is low. An interesting finding of fullness of pulse due to low diastolic pressure is to be noted in some cases of patency of the ductus arteriosus of extensive degree where a hydrodynamic situation exists somewhat comparable to that in the case of aortic regurgitation. Also it is an important fact for diagnosis that with coarctation of the aorta the blood pressure (systolic and pulse pressure) in the upper extremities is higher than that in the lower extremities sometimes to a marked degree when the coarctation is extreme.

**Roentgenologic study** Roentgen ray study of the heart and great vessels in congenital heart disease may be a great aid but it is sometimes of no help at all and serious cardiovascular defects may exist with no clear indication of their presence by roentgen ray. Positive findings by this method of examination may be however the only clue to trouble either to its existence or to the particular lesion or lesions especially in differentiating left heart involvement from right and in revealing abnormalities of the great vessels. Right ventricular enlargement may be revealed more by the so-called *coeur en sabot* or wooden shoe shape of heart shadow than by any increase in size of the cardiac silhouette (Figure 72 page 319) this is found especially when the pulmonary artery is hypoplastic (small) as in the tetralogy of Fallot but not when it is large even though the right ventricle is very big as with an atrial septal defect. Marked enlargement of the whole heart shadow is characteristic of congenital idiopathic hypertrophy of coronary anomalies (the left arising from the pulmonary artery) and of von Gierke's glycogen storage disease (see page 323). Undue prominence of the shadow of the pulmonary artery may confirm the diagnosis of patent ductus arteriosus (see Figure 80 page 339). When there is no characteristic murmur of patency of the ductus arteriosus bulging of the pulmonary arc as seen by roentgen ray strongly favors the diagnosis of a defect in the septum between the atria and the larger the bulge the more likely is the latter defect. Errors have frequently arisen in the past from relying on roentgenologic rather than on auscultatory evidence of ductus arteriosus patency. Marked dilatation of the vessels in the lung hilus shadows helps to establish the diagnosis of an interatrial septal defect (see Figure 68 page 313).

Increase in the shadow of the ascending aorta is especially the rule in the tetralogy of Fallot where the aorta is both dextroposed and abnormally capacious it may also be found to a lesser degree with coarctation of the aorta. Decrease in the ascending aortic shadow is common in the case of atrial septal defects and with aortic stenosis. Absence of the aortic arch shadow may be found if there is considerable coarctation of the aorta or a right sided arch may be visible. The esophagus and trachea may be displaced forward by a right sided aortic arch and compressed by a vascular ring. And finally notching of the ribs may be evident due to dilated intercostal arteries in cases of coarctation of the aorta (see Figure 77 page 332).

*Electrocardiographic examination* In some cases of congenital heart disease the electrocardiogram is normal or so slightly divergent from the normal that it is in no way helpful. Even negative findings are useful, however, since they tend to rule out right-sided lesions when there is uncomplicated defect of the interventricular septum, patency of the ductus arteriosus or coarctation of the aorta. There are three conditions where the electrocardiogram is especially helpful and shows characteristic changes. The more common of these three is right ventricular enlargement, usually associated either with pulmonary stenosis, most commonly found in that combination of defects already described as the tetralogy of Fallot, or with interatrial septal defect. These conditions give rise to right ventricular preponderance, often of marked degree. In fact the greatest degree of right ventricular preponderance known is found in congenital heart disease. With this abnormal right axis deviation there is found usually an abnormal increase of amplitude of the P (atrial) wave. The second characteristic electrocardiographic pattern is that showing abnormal left axis deviation due to enlargement of the left ventricle in the rare cases of tricuspid atresia; here the electrocardiogram may be the chief clue in the differentiation from the tetralogy of Fallot since both conditions cause considerable cyanosis and finger clubbing. The third characteristic electrocardiographic finding is in the case of mirror picture dextrocardia, the so-called heterotaxy (*ετερος* opposite and *ταξίς* arrangement) whether complete or isolated (that is, with or without abdominal visceral transposition also); here Lead 1 of the electrocardiogram is completely inverted and Leads 2 and 3 are reversed (Figure 65). Isolated congenital dextrocardia, as a matter of fact, has not been found to occur without other more important congenital cardiovascular defects (Roesler, 1930). It is of great importance to be certain that this electrocardiogram is caused by the position of the heart and not by an artifact due to crossing of the first two lead connections. If, as occurs in some cases, dextrocardia is associated with some defect which results in right ventricular enlargement, then the electrocardiogram will indicate a marked degree of abnormal left axis deviation, but with inverted P waves in Lead 1. In cases of the two-chambered heart (*cor biloculare*) or of the three-chambered heart with one ventricle (*cor triloculare biatriatum*) there tend to be biphasic QRS waves of wide amplitude in all three classical limb leads and in the precordial leads. Finally, as noted above, there are rare cases of congenital heart block, either complete or partial, requiring electrocardiography for confirmation. It is of interest that the ventricular rate in cases of congenital complete heart block tends to be rather high, in the fifties or sixties, as a rule, and so may obscure the disorder of rhythm until an electrocardiogram is obtained.

*Other data* *Urine* Albuminuria is common in the severer types of congenital heart disease, partly because of engorgement due to polycythemia, less often because of slight to moderate congestion from cardiac insufficiency.

*The blood* Unless there is cyanosis or infection, the blood cell counts and hemoglobin will be normal. With a complicating infection, polymorphonuclear leukocytosis is of course expected. With cyanosis and a shunt of venous blood

into the systemic circulation a polycythemia is found increasing in degree as the shunt and cyanosis increase. A red blood cell count of 6 or 7 millions is common in cases classed as the *morbus caeruleus* and in extreme cases even 10, 11 and 12 million erythrocytes have been reported. Along with this increase of red cells there is an increase of hemoglobin which usually runs

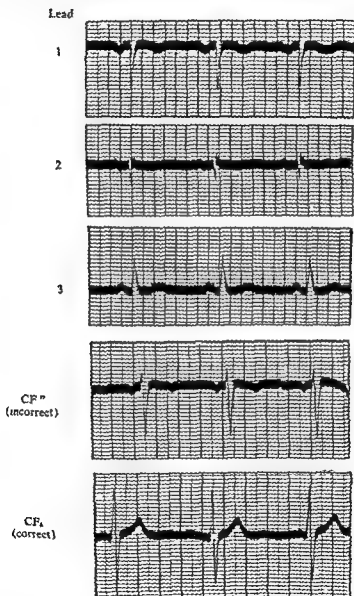


FIG. 65 Electrocardiogram (four leads) in a case of congenital dextrocardia with complete situs inversus and without other congenital defects. The first Lead "CF" taken (labeled "incorrect" above) was erroneously obtained from the left side. On discovery of the dextrocardia the correct Lead CF was taken as shown above. J.C. male age 30.



parallel, to 110 120 130, and in rare cases up to 180 or 200 per cent (25 gm) The reason for these increases is obvious Since the oxygen saturation of the hemoglobin is low because of lack of contact of a large percentage of the red cells with oxygen in the alveoli of the lungs an increase in the number of red cells occurs in order to transport sufficient oxygen to the tissues The oxygen capacity may almost double while the oxygen saturation of the blood is nearly halved the result is close to a normal amount of oxygen in the blood under favorable circumstances

The viscosity of the blood is much increased in polycythemia since viscosity is controlled chiefly by the number of cellular elements in the blood It may be increased several fold This means more work for the circulation and peripheral vasodilatation occurs in part to allow a more complete oxygen distribution to the tissues and in part to relieve the strain on the heart The actual blood volume is also increased in polycythemia the amount depending on the degree of cellular increase

The amount of oxygen and of carbon dioxide in the blood has already been referred to (Chapter 10) It is normal in cases of congenital defects without unusual communications but there are two abnormal situations dependent on the direction of the shunt venoarterial and arteriovenous

**Venoarterial shunts** An abnormally low oxygen saturation of the hemoglobin of the arterial blood is common in the case of the defects which result in venoarterial shunts it may reach even the low figure of 58 to 62 per cent (Talbot et al 1941) If about one third of the venous blood entering the right heart chambers is shunted directly into the systemic circulation the percentage of blue-colored reduced hemoglobin in the arterial blood may be increased to 20 per cent instead of the normal 1 to 5 per cent (or 4 volumes per cent instead of the normal  $\frac{1}{2}$  to 1 volume per cent) passing the threshold at which cyanosis appears A greater shunt than this yields still more reduced hemoglobin in the arterial blood and a greater degree of cyanosis in the case already referred to with very low oxygen saturation of the arterial blood it was estimated that 75 per cent of the blood in the heart chambers traversed the right to left shunt (Talbot et al 1941) However it is possible for a smaller shunt than that of one third to produce cyanosis provided there is an abnormally high red cell and hemoglobin content It is not the percentage but the total amount of reduced hemoglobin whether originating by shunt in heart or lungs or by peripheral stasis that is primarily responsible for the abnormal color of the blood made obvious by dilated capillary vessels If in the capillaries there are 5 gm or more of reduced hemoglobin per 100 cc of blood cyanosis will result With normal red cell and hemoglobin content 3.5 to 4 volumes of reduced hemoglobin in the arterial blood will yield 6.5 or more volumes per cent in the capillary blood (or 5 gm per 100 cc) With polycythemia and an increased oxygen content capacity of the blood due to increased hemoglobin the same amount of reduced hemoglobin may be present in the capillary blood to cause cyanosis even though the actual percentage of oxygen unsaturation of the arterial blood due to a smaller shunt may be only 10 or

15 per cent If it were possible for severe anemia and a very low hemoglobin content (and therefore a low oxygen capacity of the blood) to develop in cases of venoarterial heart shunts it might be impossible to reach the stage of cyanosis no matter how little the oxygen saturation of the arterial blood might be because as much as 5 gm of reduced hemoglobin could not be produced in 100 cc of capillary blood The occurrence of severe anemia in the morbus caeruleus is however not likely since it would seem to be incompatible with life

Two other factors often enter into congenital heart disease with a venoarterial shunt to decrease the oxygen content of the capillary blood One of these is the structural and functional state of the lungs a factor which even with cardiac catheterization makes difficult any accurate estimation of the amount of the shunt Polycythemia and thickening of the alveolar capillaries are inevitable accompaniments of advanced morbus caeruleus Failure of proper oxygenation of the blood in the lungs may add its effect to that of a venoarterial shunt in reducing the oxygen content of arterial and capillary blood and in causing cyanosis The second additional factor consists of the slowing of the peripheral circulation which decreases still further the oxygen content of capillary blood in the morbus caeruleus The content of oxygen in the venous blood follows that of the arterial blood in such cases but is several volumes per cent lower An interesting and important factor that helps to decrease the oxygen unsaturation of the blood in cases of right to left shunt is the development of a somewhat compensatory collateral bronchial circulation The bronchial arteries and their branches course along the bronchi and bronchioles parallel to the pulmonary arteries but with a much more tortuous course They may become considerably enlarged in cases of the morbus caeruleus particularly the tetralogy of Fallot and thus may bring a good deal of blood to the lungs for oxygenation This bronchial circulation may appear quite clearly in the x ray pictures of the chest even though the pulmonary artery and its branches are much diminished in such shadows

The carbon dioxide content of the arterial and venous blood in the morbus caeruleus tends to be low rather than high (as one might at first have expected it to be) This is probably due to increased ventilation whereby the carbon dioxide which is thirty times more diffusible than oxygen is pumped out of the blood in the lungs and also to a tissue acidosis from faulty metabolism (due to the poor circulatory state) with retention of bicarbonate in the tissues

An interesting effect of venoarterial shunts on tests of the rate of the circulation (see Chapter 10) is worthy of note In cases with such shunts in the absence of heart failure not only is arm vein to tongue arterioles time much reduced below the usual normal because of cutting out the lesser circulation from a good deal of the blood flow but the total round trip (arm to tongue or arm vein to leg artery) time may actually be or seem to be slightly faster than the arm to lung time as in tests with ether

**Arteriovenous shunts** The other particular influence of congenital cardiac defects on the blood gases is in the case of arteriovenous shunts particularly

atrial septal defects patency of the ductus arteriosus and interventricular septal defects. If large enough these defects cause by their admixture of arterial with venous blood abnormally high oxygen and abnormally low carbon dioxide content of the venous blood entering the pulmonary circulation (Burwell, Lippinger and Gross 1940 and 1941).

**Cardiac catheterization** Catheterization of the heart chambers and pulmonary artery has been discussed in Chapter 10 but one should add here that perhaps its most useful application is in the diagnosis of congenital defects. A higher blood content of oxygen than normal is found in the right atrium in the case of an atrial septal defect in the right ventricle in the case of a ventricular septal defect and in the pulmonary artery in the presence of a patent ductus arteriosus. Moreover, the catheter can be passed under fluoroscopy through an atrial septal opening into the left atrium or into the aorta in the tetralogy of Fallot (see Figure 56 pages 228 and 229).

**Course and prognosis** The course and prognosis of congenital heart disease vary with the type. In cases with relatively unimportant lesions where there are no shunts for example abnormal chordae tendineae and valve cusps simple dextrocardia pericardial anomalies slight to moderate coarctation of the aorta and in cases with lesser degrees of arteriovenous shunt through uncomplicated patent ductus arteriosus or interventricular septal defect life may not be handicapped or shortened and with all these conditions old age has been comfortably reached with no cardiac disability due to these defects. Even these lesions are however somewhat perilous because of the possibility of their being the site of bacterial infection especially of streptococcal nature. This infectious invasion serious and in former days so often fatal is not rare particularly in the case of bicuspid aortic valves of ventricular septal defects and of patent ductus arteriosus. In Maude Abbott's series 9 of 32 cases (28 per cent) of the first named 13 of 50 cases (26 per cent) of the second and 21 of 92 cases (23 per cent) of the last named developed subacute bacterial endocarditis or endarteritis. Gelfman and Levine (1942) found the incidence of acute and subacute bacterial invasion in patients over the age of two years with the more common congenital cardiovascular defects as follows: ventricular septal defects (Roger's disease) 57.1 per cent of 14 cases; patent ductus arteriosus 28.6 per cent of 14 cases; pulmonic stenosis 29.4 per cent of 17 cases; bicuspid aortic valves 21.2 per cent of 52 cases; tetralogy of Fallot 28.6 per cent of 7 cases; coarctation of the aorta 10 per cent of 10 cases and *atrial septal defects none among 45 cases*.

In the case of the more serious defects the course is difficult and the prognosis grave. Both the difficulty of the course and the seriousness of the prognosis depend on two factors. The first of these factors is the degree of anoxemia which is indicated to a certain extent by the degree of cyanosis. This anoxemia affects all organs of the body especially the brain and the heart. The second factor is the amount of direct strain on the heart. Two other points are to be remembered. Cyanosis does not usually appear early in infancy and yet the prognosis at this early age may be bad. Moreover, anoxemia

and cyanosis are not strictly comparable since there may be a sufficient quantity of oxygen in the blood for the tissues if there is a polycythemia and yet there may be also enough reduced hemoglobin to cause cyanosis. This explains why many cyanotic individuals are not dyspneic.

The most serious lesions like ectopia cordis abdominalis, uncomplicated transposition of the great vessels, the two chambered heart and pulmonary or aortic atresia with closed ventricular septum may be so crippling that a miserable existence is possible for but a few days, weeks or months at best.

Sudden unexpected death is not a rare termination in the case of infants and children with congenital heart disease even in those who show little or no evidence of the condition during life (Levinson 1941).

The less grave cases of the morbus caeruleus may occasionally survive to adult life or even into middle age if they live carefully and are fortunate enough to escape serious complications. Some striking cases are on record of long survival especially one of a noted musician who lived a useful life to the age of 59 years and 8 months in spite of the tetralogy of Fallot and another of a woman with marked pulmonary valve stenosis and atrial septal defect who lived actively until she died of right heart failure at the age of 74 years and 11 months. Both diagnoses were confirmed by postmortem examination and both patients showed cyanosis and clubbing of the fingers from early childhood (White and Sprague 1929, White Hurst and Fennel 1950). Limitation of activity is almost always enforced by the morbus caeruleus because of dyspnea, weakness and cerebral symptoms.

**Complications.** The chief complications of congenital heart disease are infections especially pneumonia, cerebral attacks—syncope, coma, convulsions and hemiplegia due to thrombosis or hemorrhage—bacterial endocarditis or endarteritis and congestive heart failure. These complications are often fatal. An analysis of 453 autopsied cases of all ages of congenital heart disease in Boston hospitals gave a total incidence of 6.6 per cent affected by subacute bacterial endocarditis or endarteritis as compared with 16.8 per cent among those over the age of 2 years (Gelfman and Levine 1942). This dread disease is now fortunately in major part preventable or curable because of the advance in surgical therapy and of the introduction of penicillin. An uncommon complication in cases with septal defects is cerebral infarction or abscess from paradoxical embolism.

**Treatment.** In the first two editions of this book (1931 and 1937) it was stated that there is no curative treatment, surgical or medical, for congenital cardiac defects, but notable advances have been made in the last twelve years in several particulars: (1) patency of the ductus arteriosus is now curable by surgery; (2) coarctation of the aorta can also be corrected surgically in nearly all young cases; (3) a vascular ring constricting trachea and esophagus can be broken; (4) certain instances of the morbus caeruleus, in particular the tetralogy of Fallot, can be greatly helped by surgery; and (5) penicillin can cure many of the cases infected by the alpha hemolytic streptococcus. And other advances are in the offing.

In some cases of congenital heart disease no special care is needed though even the least serious case should be protected against infection to avoid complicating bacterial invasion and pneumonia. Since the teeth and gums harbor in particular the alpha hemolytic streptococcus the cause of subacute bacterial endocarditis and endarteritis in the vast majority of cases it is wise to protect by penicillin the patients with congenital cardiovascular defects who are to be subjected to dental extractions or other extensive treatment. 300 000 units should be given intramuscularly 1 hour before the dental treatment and again 3 hours after.

Tonsillectomy is probably advisable in childhood though not in infancy provided the tonsils are diseased and provided there is not too great a risk for operation. Protection from fatigue and care to provide suitable diet are to be urged for the cyanotic cases and for those with much heart strain. Finally complications of congestive failure, cerebral lesions and infections are to be treated as such by rest in bed, digitalis as required, penicillin and other measures. If the victim of congenital heart disease is well protected his life may sometimes be prolonged for many years.

**Differential diagnosis.** Congenital heart disease may resemble two other conditions, acquired heart disease and pulmonary disease. It is to be differentiated from the former by the history of involvement of the heart from birth if that is reliably obtained and by the characteristic signs—certain murmurs, heart shape, cyanosis, clubbing of the fingers and typical electrocardiograms when such exist (as described above), in a few instances the differentiation is very difficult. Acquired heart disease, especially rheumatic, subacute bacterial and coronary, may be superimposed on congenital cardiovascular defects.

It is more difficult to differentiate pulmonary disease, such as pulmonary fibrosis with emphysema or pulmonary endarteritis, when it is attended by cyanosis, polycythemia and clubbing of the fingers, from the morbus caeruleus of congenital heart disease, especially if the latter happens not to show characteristic murmurs, electrocardiograms or orthodiagrams. Great care must be taken in analyzing such cases.

The discovery of congenital anomalies elsewhere in the body favors somewhat the diagnosis of congenital cardiovascular defects when the differentiation of the type of heart disease is difficult or obscure.

The more common individual congenital cardiovascular defects should in the present day and age (in striking contrast to a generation ago) usually be differentiated with ease except in infancy. It seems likely that the ratio of diagnosability of individual defects during infancy to that after infancy is about 30 per cent as compared to 90 per cent. Rare defects are however as a rule undiagnosable.

### INDIVIDUAL CONGENITAL CARDIOVASCULAR DEFECTS

It has become possible during the present generation clinically to recognize the majority of congenital cardiovascular defects and therefore they have

assumed an increasing importance in the practice of medicine. They will be presented in the following order: congenital malposition of the heart; congenital abnormalities of the cardiac chambers and septal defects; congenital myocardial disease; congenital endocarditis and valvular defects; congenital pericardial defects; congenital anomalies of the great arteries and veins; and congenital anomalies of the coronary arteries.

## CONGENITAL MALPOSITION

Congenital malposition of the heart includes dextrocardia and ectopia cordis.

Congenital dextrocardia is of two main types occurring with about equal frequency. (1) In the first type without transposition the heart is slightly rotated and rests in the right side of the chest. The left chambers lie to the left and anteriorly, the right chambers lie to the right and posteriorly, and the apex is made up either of the right ventricle or of the right side of the common ventricle. Almost invariably in this type there is some serious associated congenital anomaly like a single ventricle. The prognosis and course of the congenital heart disease depend on these associated anomalies and not on the dextrocardia. (2) The other variety of congenital dextrocardia is that attended by transposition of the chambers whereby the left chambers lie on the right side and form the right border and apex and the right chambers lie on the left side. Almost invariably the abdominal viscera are also transposed (complete heterotaxy or situs inversus). With this type of congenital dextrocardia that is the mirror type there are usually no other congenital cardiac defects at least of serious nature unless the dextrocardia is isolated that is occurring without associated general transposition of other organs (Roesler 1930). Dextrocardia uncomplicated by other cardiovascular defects is unimportant clinically. It is discovered accidentally on routine physical or roentgen ray examination or even by electrocardiography and in no way affects activity or duration of life. A pathognomonic sign of this mirror type of congenital dextrocardia is electrocardiographic complete inversion of Leads 1 and aVR and transposition of Leads 2 and 3, aVL and aVF and of the precordial leads (Figure 65). An interesting complication of the situs inversus which may in some cases be regarded as a stigma of an associated congenital maldevelopment is bronchiectasis which was found in 5 of the 23 cases of the situs inversus (21.7 per cent) recorded at the Massachusetts General Hospital in the fifty years from 1886 to 1936 while of the general hospital population over that period of time bronchiectasis was diagnosed in but 0.3 per cent (Churchill and Adams 1937).

Ectopia cordis, a very rare defect, consists of the malposition of the heart outside of the thoracic cage either in the abdomen or actually projecting outside the body wall. It is of academic interest only since attempts at surgical correction have as yet been unsuccessful and life is almost invariably very brief, a matter of a few days or at best a few weeks.

## CONGENITAL ABNORMALITIES OF CARDIAC CHAMBERS SEPTAL DEFECTS

Congenital abnormalities of the cardiac chambers include complete and partial absence of atrial and ventricular septa. These defects may be unimportant, discovered only at postmortem examination after a long and active life and unsuspected before death, or they may be of great importance, permitting only a few hours or days of existence after birth. The degree of the defect and complicating abnormalities determine the importance of each lesion.

### Atrial Septal Defects

Atrial septal defects are much more numerous than any other anomaly in congenital cardiovascular disease. In Abbott's series of 1 000 cases there were 402 individuals with openings between the atria which included true (not slit like) patency of the foramen ovale (290 cases), persistent ostium primum in the lower part of the septum (36 cases), persistent ostium secundum in the upper part (19 cases), multiple defects (28 cases), and complete absence of the septum in the biloculate heart (14 cases) or in the triloculate heart with one atrium and two ventricles (15 cases).

Patency of the foramen ovale is of the least importance and greatest frequency of all congenital cardiac abnormalities. The foramen ovale is a valve like opening between the atria developing from the ostium secundum of the embryo and functioning in fetal life to allow the passage of considerable blood directly from venous to arterial circulation without going through the lungs. It closes soon after birth and usually becomes sealed within the first three months of life. In many cases it remains anatomically slightly patent as a valve slit but as such it is functionally inactive. When the slit opening is small the patent foramen ovale is of absolutely no importance, but if it is moderately large and the right atrial pressure is much raised, venous blood may pass into the left atrium and even occasion slight cyanosis. Clinically unimportant patency of the foramen ovale has been reported in nearly one quarter of all autopsied cases (with a range from about one eighth to one third).

In a few cases the foramen ovale remains really patent and in such cases it may prove to be of some importance. In one series of 500 hearts (250 from white and 250 from Negro subjects) probe patency of the foramen ovale was found in 85 cases (17 per cent) while in only 2 cases (0.4 per cent) did the valvula foraminis ovalis actually fail completely to cover over the foramen ovale (Seib, 1934). Wide patency is usually associated with and probably caused by other more important congenital abnormalities, such as pulmonary stenosis or transposition of the great arterial trunks, or with acquired mitral stenosis, and these other defects determine the course and prognosis. Of a

The terms "atrial septum" and "ventricular septum" are used interchangeably with "inter atrial septum" and "interventricular septum" respectively.

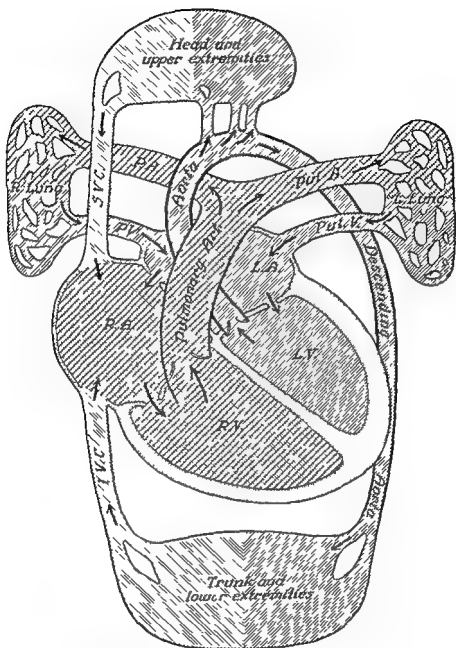


FIG 66 Diagram of atrial septal defect (Kindness of Dr Helen Taussig Johns Hopkins Hospital Baltimore and The Commonwealth Fund New York City )





series of 290 cases of patent foramen ovale (Abbott 1931) only 40 were instances of pure or primary patency

Atrial septal defects of importance are those that involve relatively large areas of the septum (1) The *primitive ostium primum* in the lower part of the septum (36 cases in Abbott's series of 1 000 individuals with congenital cardiovascular defects 18 of the 36 complicating other defects) or (2) the *primitive ostium secundum* (from which the foramen ovale develops) in the upper part of the septum (19 cases of Abbott's series 9 of which complicated other defects) or (3) *absence of the entire atrial septum* giving a three chambered or *triloculate heart* (*cor triloculare biventriculare*) if there are two ventricles or a two-chambered or *biloculate heart* (*cor biloculare*) if there is but one ventricle (15 cases of the former and 14 of the latter in Abbott's series) Females showed a slight preponderance (44 to 35) in these three categories of atrial septal defect in Abbott's series All these lesions are more serious than patency of the foramen ovale persist from an earlier stage of fetal life and are often complicated by other anomalies Persistence of the ostium primum is not only more common than that of the ostium secundum but it is also much more serious (Figure 66 opposite page 310)

The explanation of the increase in size and work of the right heart chambers in these cases is that extra blood often in large amount enters the right atrium from the left atrium through the septal defect this direction of flow has been assumed to be due to a slightly higher pressure in the left atrium but Uhley (1942) has shown that an important perhaps the most important cause of this direction of flow is the effect of gravity the right atrium being anatomically situated below the left, the septum lying more or less horizontally

In the cases of persistence of the primary and secondary ostia there may be no symptoms or signs and the subjects may live fairly long lives though not so long as those with foramen ovale patency Enlargement and failure of the right ventricle are however common Loud systolic murmurs rarely accompanied by thrills are found in most of the cases chiefly in the pulmonary valve area Years ago they were ascribed to the septal defect itself but it has become evident that they are due to the dilatation of the pulmonary artery which is secondary to the increased pulmonary circulation or to a complicating mitral valve defect With large atrial defects the electrocardiogram shows marked right axis deviation (Figure 67) and the roentgen ray shows enlargement of the right atrium right ventricle and pulmonary artery and its branches large and small and also hypoplastic aorta (Figure 68) it is probable that in some cases at least twice as much blood passes through the pulmonary circulation as through the systemic Paradoxical embolism may occur Cyanosis is infrequent but may appear as an occasional or terminal event when the right atrial pressure becomes greater than that in the left atrium or constantly if there is a complicating pulmonary stenosis

An analysis of 53 cases of atrial septal defects 10 with necropsy control (Bedford Papp and Parkinson 1941) showed a preponderance of females in the ratio of 4 to 1 the age of death mostly from 30 to 50 years and the

cause of death in the autopsied cases congestive heart failure in 3 pulmonary infarction in 2 embolism (one paradoxical) in 2 subacute bacterial endocarditis (a very rare complication) in only 1, bronchopneumonia in 1 and surgical operation in 1 the upper part of the septum was involved in 8 of these 10 cases A pulmonary systolic murmur was found in 32 of the entire series and an accentuated pulmonary second sound in 31, followed by a diastolic murmur (probably due to a stretching of the valve ring) in 10 Slight or late cyanosis was present in 31 cases Excessive pulsation of the lung hilum was noted by roentgen ray in 31 of the 50 cases so studied but a hilar dance was observed in only 5 Normal rhythm was the rule being present in 47 cases

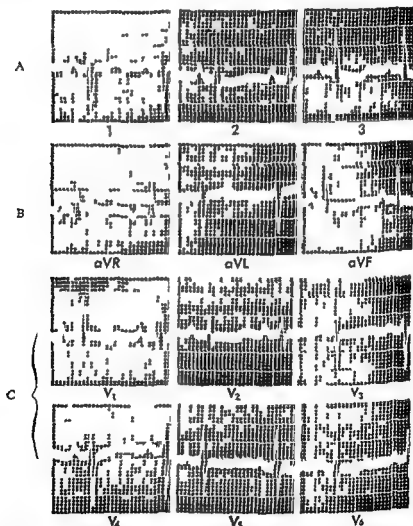


FIG 67 Electrocardiogram in a case of atrial septal defect female age 26 (4) Bipolar limb leads 1 2 and 3 (B) unipolar limb leads aVR aVL and aVF (C) six precordial leads  $V_1$  to  $V_6$  inclusive Time = 0.04 and 0.20 second amplitude 1 mm = 0.10 mv

Right ventricular preponderance was present in the electrocardiogram in 41 cases and complete right bundle branch block in 5 others

When there is but one atrium life is generally much limited but some cases of remarkable longevity are on record with few symptoms or signs Cyanosis is the rule thrills and murmurs are infrequent and dyspnea is inconstant Of 5 cases with one atrium and two ventricles cited by Abbott one lived to the age of 31 years the mean duration of life was 6 years Of 9 cases with



FIG 68 Roentgenogram of thorax of case of congenital defect of the interatrial septum showing extreme degree of dilatation of the pulmonary artery and its branches right and left along with enlargement of the right ventricle Note the shadows of cross sections of arteries Small aorta (Kindness of Dr Hugo Roesler Temple University Philadelphia)

one atrium and one ventricle the oldest case was 16 years at death and the mean age was  $3\frac{1}{4}$  years

A very interesting association is that of *mitral stenosis with a defect of the interatrial septum* (Abbott 1915 Lutembacher 1916) There is a combined effect of both lesions The left atrium tends to remain small and the right atrium becomes very large receiving as it does the extra blood from the left atrium as well as from the great veins There have been noted murmurs over the sternum or just to the left presystolic and systolic in time ascribed to the passage of blood through the septal defect but it is naturally difficult to differentiate such murmurs from those due to the mitral valve disease and

transmitted thither certainly the most common cause of the basal systolic murmur in such cases is dilatation of the pulmonary artery which is invariably present. The congenital deficiency of the atrial septum has been given credit for relieving somewhat the burden imposed on the pulmonary circulation and right ventricle by marked mitral stenosis and thereby aiding the prolongation of life. Remarkable cases of this combination of mitral stenosis and atrial septal defect are on record including that of a woman of 74 years of age who had passed successfully through eleven pregnancies and three abortions (Firket 1880) a woman of 61 years who had gone through seven pregnancies without heart failure (Lutembacher 1916) and two other cases aged 74 and 62 years respectively (Bonnabel 1906). However interatrial septal defects alone if large impose a serious burden on the right heart and pulmonary circulation and therefore it does not appear likely that they can aid much in relieving the heart or lungs in the presence of mitral stenosis except probably to prevent attacks of acute pulmonary edema which are an infrequent but distressing complication of tight mitral stenosis when the heart beats too rapidly.

A large atrial septal defect is always to be suspected when there is the combination of a loud pulmonary systolic (not continuous) murmur, marked prominence of the pulmonary artery and lung hilus shadows and small aortic shadow by roentgen ray and pronounced right ventricular preponderance by electrocardiogram in a person in fairly good health save for a variable amount of dyspnea. In differential diagnosis it may be said that the *cor pulmonale* due to pulmonary disease or endarteritis gives less right axis deviation and less lung hilus engorgement while mitral stenosis is of course attended by its characteristic diastolic murmur.

Surgical correction of uncomplicated but important atrial septal defects is now on trial and has been successful in a few cases (Murray 1948).<sup>3</sup> Correction of the atrial septal defect was done by passing sutures through the anterior wall beginning to the right of the aorta and pulmonary artery to emerge posteriorly through an area between the superior vena cava and right pulmonary veins. These sutures were tied together posteriorly drawn taut and tied down firmly thus compressing the anterior and posterior walls of the atria. In one of the cases described the right atrium diminished to at least one half its size in two minutes the patient's condition was improved.

### Ventricular Septal Defects

Next in frequency after atrial septal defects come ventricular septal defects of which in Abbott's series there were 315 instances including localized openings isolated or complicated (274 cases) complete absence of the septum in the biloculate heart (14 cases) and in the triloculate heart with one ventricle and two atria (27 cases).

Localized ventricular septal defects are generally associated with other

<sup>3</sup> In March 1951 Murray (personal communication) stated that he had performed the operation of closure of an atrial septal defect in seven cases with considerable improvement in three some improvement in two and death in two.

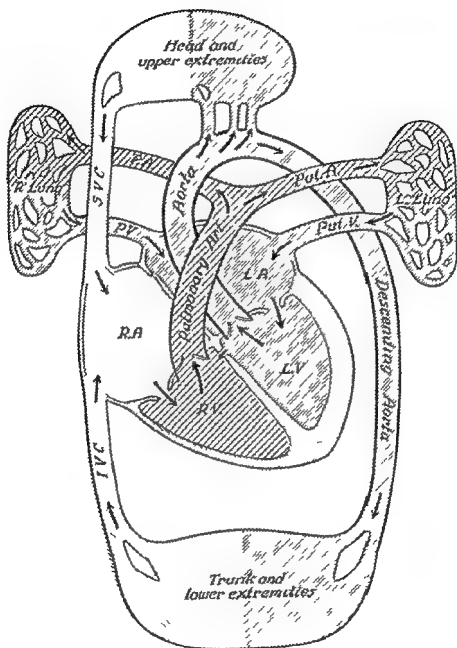


FIG 69 Diagram of ventricular septal defect (Kindness of Dr Helen Taussig Johns Hopkins Hospital Baltimore and The Commonwealth Fund New York City)

transmitted thither certainly the most common cause of the basal systolic murmur in such cases is dilatation of the pulmonary artery which is invariably present. The congenital deficiency of the atrial septum has been given credit for relieving somewhat the burden imposed on the pulmonary circulation and right ventricle by marked mitral stenosis and thereby aiding the prolongation of life. Remarkable cases of this combination of mitral stenosis and atrial septal defect are on record including that of a woman of 74 years of age who had passed successfully through eleven pregnancies and three abortions (Firket 1880) a woman of 61 years who had gone through seven pregnancies without heart failure (Lutembacher, 1916), and two other cases aged 74 and 62 years respectively (Bonnabel 1906). However interatrial septal defects alone if large impose a serious burden on the right heart and pulmonary circulation and therefore it does not appear likely that they can aid much in relieving the heart or lungs in the presence of mitral stenosis except probably to prevent attacks of acute pulmonary edema which are an infrequent but distressing complication of tight mitral stenosis when the heart beats too rapidly.

A large atrial septal defect is always to be suspected when there is the combination of a loud pulmonary systolic (not continuous) murmur marked prominence of the pulmonary artery and lung hilus shadows and small aortic shadow by roentgen ray and pronounced right ventricular preponderance by electrocardiogram in a person in fairly good health save for a variable amount of dyspnea. In differential diagnosis it may be said that the *cor pulmonale* due to pulmonary disease or endarteritis gives less right axis deviation and less lung hilus engorgement while mitral stenosis is of course attended by its characteristic diastolic murmur.

Surgical correction of uncomplicated but important atrial septal defects is now on trial and has been successful in a few cases (Murray 1948).<sup>3</sup> Correction of the atrial septal defect was done by passing sutures through the anterior wall beginning to the right of the aorta and pulmonary artery to emerge posteriorly through an area between the superior vena cava and right pulmonary veins. These sutures were tied together posteriorly drawn taut and tied down firmly thus compressing the anterior and posterior walls of the atria. In one of the cases described the right atrium diminished to at least one half its size in two minutes the patient's condition was improved.

### Ventricular Septal Defects

Next in frequency after atrial septal defects come ventricular septal defects of which in Abbott's series there were 315 instances including localized openings isolated or complicated (274 cases) complete absence of the septum in the biloculate heart (14 cases) and in the triloculate heart with one ventricle and two atria (27 cases).

Localized ventricular septal defects are generally associated with other

<sup>3</sup> In March 1951 Murray (personal communication) stated that he had performed the operation of closure of an atrial septal defect in seven cases with considerable improvement in three some improvement in two and death in two.

congenital defects and are almost invariably found at the base of the heart just below the aortic valve in the region of the so-called undefended or fibrous space. Of the series of 274 cases collected by Abbott the ventricular septal defects were in this basal position in all but 17 and these 257 basal defects complicated other abnormalities in 207 cases leaving 50 instances of the pure defect. Seven of the 207 complicated cases had but a right sided (dextro-) position (Rechtslage) of the aorta as an additional defect, constituting the Eisenmenger complex while 51 had pulmonary stenosis with aortic dextroposition in 32 constituting the tetralogy of Fallot. These complications are important in that they favor cyanosis the dextroposition of the aorta is especially significant in this respect. The sexes are about equally represented in pure interventricular septal defects of Abbott's series of 50 cases 21 were male 26 were female and the sex of 3 was not stated.

The pure ventricular septal defect is usually small and more or less circular or oval 1 to 2 cm in diameter (Figures 69 and 70). Its septal edge is often thickened and fibrous and the endocardium of the right ventricular wall opposite the opening is also similarly affected probably by the repeated impact of the blood stream from the left ventricle. The right ventricle is usually somewhat enlarged (hypertrophied and dilated) and the pulmonary artery is slightly dilated the left ventricle also may be bigger than normal. The shunt through the uncomplicated septal defect is arteriovenous that is, left to right except under unusual conditions.

There are no symptoms of pure ventricular septal defects unless they are very large and in rare cases there are no signs. Usually however there is a loud blowing systolic murmur heard best just to the left of the midsternum and not widely transmitted. When the murmur is very loud there is a palpable thrill also but this is occasionally absent. Cardiac enlargement may or may not be evident on physical examination and by roentgen ray. The electrocardiogram is normal except in a few cases with abnormal right axis deviation and in rare cases in which the septal defect is associated with abnormality of the atrioventricular bundle (of His) with resulting congenital heart block. Cyanosis is rare in the case of uncomplicated ventricular septal defect and is practically only a terminal condition the shunt being reversed to become venoarterial or right to left when the right ventricular pressure exceeds that in the left ventricle in pneumonia or some other such complication. Infrequently when the septal defect is large the whole heart may be much increased in size and fail with characteristic congestive signs and symptoms including dyspnea.

An isolated interventricular septal defect has been called *Roger's disease* (Roger 1879) and the murmur caused by this defect has been called *Roger's murmur*.



The following conclusions of this original publication are of interest (translation by myself)

1 There is a *developmental defect of the heart* from which cyanosis does not result in spite of the communication between the two ventricular cavities and in spite of the free mixture of venous blood with arterial blood. This congenital abnormality which is compatible even with a long life is a simple one without the coexistence of congenital pulmonary stenosis. It consists of a defect (opening) in the interventricular septum.

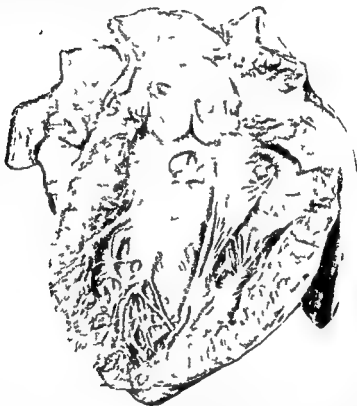


FIG 70 Photograph of the heart of a boy showing a congenital interventricular septal defect of small size just below the aortic valve. The child had a typical loud systolic murmur (Roger's murmur) with thrill at the left border of the sternum maximal in the third and fourth intercostal spaces.

"2 It is important to distinguish this cardiac anomaly which I have recently been the first to study clinically not only from other malformations but especially from acquired heart disease. It is revealed only on auscultation by a physical sign with very special characters: this is a long loud murmur (produced by the passage of blood through the interventricular opening and directly into the pulmonary artery or the aorta, the site of which is frequently abnormal in these cases). This murmur is uncomplicated by other murmurs; it begins with systole and is prolonged to such an extent that it entirely covers the natural tic-tac of the normal heart sounds. It has its maximum intensity neither at the apex (as in the case of

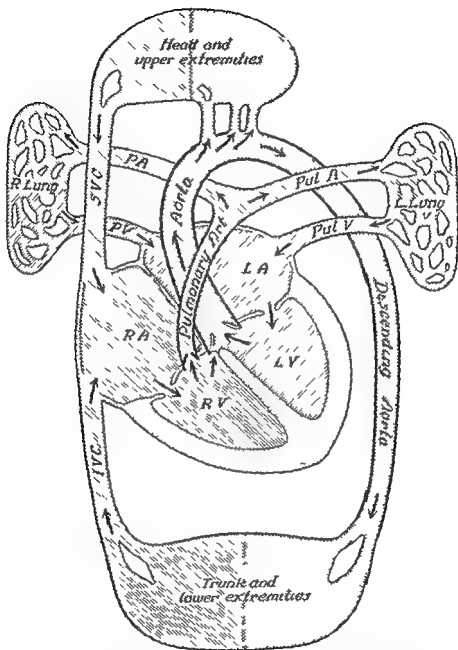


FIG 71 Diagram of tetralogy of Fallot (Kindness of Dr Helen Taussig Johns Hopkins Hospital Baltimore and The Commonwealth Fund New York City)



lesions of the auriculoventricular orifices) nor at the base to the right (as in aortic stenosis) nor to the left (as in pulmonary stenosis) but over the upper third of the precordial region. It is chiefly median in position like the septum itself and from this central point it diminishes in intensity uniformly as one moves the stethoscope over the chest. The murmur is not transmitted to the vessels. It coincides with no other sign of organic disease except the *harsh thrill* which accompanies it. This murmur is the *pathognomonic sign of an interventricular septal defect*.

3 The differential diagnosis of this malformation (until now unrecognized or confused with other congenital or acquired lesions) will be henceforth rendered easy by attentive comparison of the physical signs. These signs vary in number, site and characteristics in heart disease when structural changes are multiple, progressive and changing; while the murmur in question like the permanent unchanging lesion causing it remains without modification for an indefinite time. The same statement is true in comparing this murmur with signs of functional disorders: such signs are very variable according to the diverse periods of cardiac weakness and they are totally dissimilar in their acute or chronic nature from the constant signs of defective interventricular septum which change hardly at all with the years and increase only very slowly and almost insensibly.

4 The consideration of the age of the subject is a capital point in the diagnosis. Endocarditis, for example, shows itself almost never in infancy before the age of two years and on the other hand the anemia of very young children is almost never attended by a heart murmur. The result is that a murmur in a nursing infant is almost a certain indication of an anomaly of the heart or great vessels.

5 The prognosis is in general less grave in the malformation described above than in other organic diseases of the heart in which the danger for children is greater and nearer, permitting hopes for scarcely more than another decade of life. In spite of the presence of an uncomplicated interventricular septal defect individuals can reach and even surpass the average duration of human life.

6 An exact diagnosis ordinarily demands in heart disease an active persistent treatment. If on the other hand there is a congenital malformation of the heart vigorous treatment is useless and even harmful. To show thanks to precision in diagnosis when to act in one case and when to refrain in another is to render a service not only to physicians but also to patients.

It is of interest to note that Roger first described the condition and murmur that go by his name without having correlated in the same patients clinical and postmortem data. He had made observations clinically and pathologically but not in the same cases. Later, however, his deductions were confirmed.

Although an interventricular septal defect is theoretically not a serious lesion it is a handicap which shortens life. In Abbott's series of 50 pure cases the mean duration of life was only 14½ years, the oldest case being 49 years old. One of the chief reasons for this shortening of life has certainly been in the past subacute bacterial endocarditis which Gelfman and Levine (1942) found to have complicated 57 per cent of 14 autopsied cases. With prophylactic use of penicillin and of other new specific therapy against infections this situation will be radically changed and the prognosis will doubtless be very much brighter especially since the septal defect itself causes

relatively little strain on the heart. Protection of such a patient is especially needed at the time of dental extraction when 300,000 units of penicillin should be injected intramuscularly 1 hour before the extraction and again 3 hours after to get rid of any alpha hemolytic streptococci that may get into the blood stream. If subacute bacterial endocarditis is already present involving the edge of the defect in the right ventricle or the tricuspid valve or adjacent ventricular endocardium opposite the opening penicillin in large dosage (800 000 to 1,000 000 units a day) should be given for several weeks or if ineffective multiplied several times or supported or replaced by streptomycin. For details of this therapy consult Chapter 15 Subacute Bacterial Endocarditis.

Treatment of a pure isolated ventricular septal defect by surgery was hardly dreamed of when the first three editions of this book were published but now it is only a matter of time before such correction becomes a practical routine already animal experimentation has demonstrated its possibility and the first successful attempts have been made in man (Murray 1948)<sup>4</sup>. The technic as described by Murray consisted of introducing a strip of fascia lata into the right ventricle and attaching it to the septum. The details of this delicate operation are described by him in the *Annals of Surgery*, 1948 XXVIII 843.

Still more important will some day be the prevention of this as well as other congenital cardiovascular anomalies by the prevention or early cure of diseases virus (like rubella) and otherwise that beset the mother during the critical stage of the fetal heart development in the first trimester of pregnancy.

**The tetralogy of Fallot.** This commonest of all combinations of congenital cardiac defects and one of the most serious has already been presented in part as an interesting and characteristic malformation in the early pages of this chapter (page 290 and Figure 64 page 299) but it belongs in the group of ventricular septal defect variations and so will be further discussed here (Figure 71). As noted above the four essentials of this relatively common anomaly are (1) a high ventricular septal defect (2) a dextroposed aorta overriding the septal defect (3) stenosis of the pulmonary valve or of the right ventricular infundibulum below it and (4) a much hypertrophied right ventricle. It was encountered in 85 of Abbott's 1 000 autopsied cases of congenital defects of heart and great vessels. There are always cyanosis and finger clubbing from earliest childhood often intense the cyanosis being increased by exercise which readily distinguishes it from the slaty blue color of argyria which is decreased when the skin flushes after exercise. Shortness of breath a tendency frequently to squat weakness and faintness or even syncope are usual symptoms. A moderate to loud pulmonary systolic murmur on auscultation blunt shoe shaped heart with prominent aorta and decreased pulmonary vascular shadow on x ray examination (Figure 72) and marked

<sup>4</sup> By March 1951 Murray (personal communication) had operated to close ventricular septal defects in 13 cases with clear evidence of success in 7 (disappearance of murmur decrease of heart size abolition of shunt as shown by cardiac catheterization and increase of energy) 3 cases died.

right ventricular preponderance by electrocardiogram (Figure 73) complete the diagnostic evidence. Polycythemia and excessive hemoglobin even up to double the normal are in accord with the intensity of the cyanosis. Cardiac catheterization quickly reveals the dextroposed aorta into which the catheter

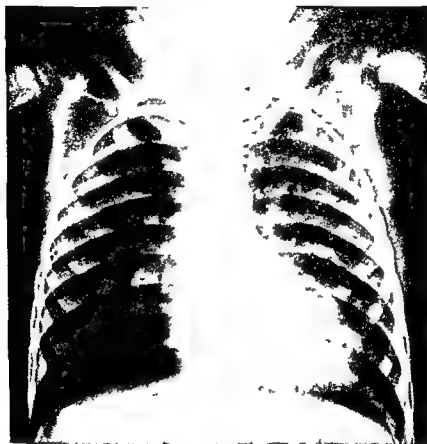


FIG 72 Roentgen film of the thorax in a case of tetralogy of Fallot

readily passes. There may be the complication of patency of the ductus arteriosus with the tetralogy of Fallot and if so there is much less cyanosis. There is in such cases a continuous murmur to the left of the sternum with the aorta in its ordinary position but with a right sided aorta the murmur is to the right of the upper sternum.

The prognosis of the tetralogy of Fallot is generally bad for a long life the average duration in Abbott's series of 85 cases being 12 years but a few patients reach middle age and one established the record of 59 years and 8 months (White and Sprague 1929). Fatal complications include cerebral abscess, cerebral thrombosis, bacterial endocarditis, respiratory infections and right heart failure.

The treatment was stated in the first three editions of this book to be only ordinary common sense protection of a cardiac cripple but in the few years that have elapsed since then a great advance has been recorded Blalock and Taussig in 1945 introduced a surgical operation that has greatly ameliorated the symptoms and signs of the disease although they have not cured it The

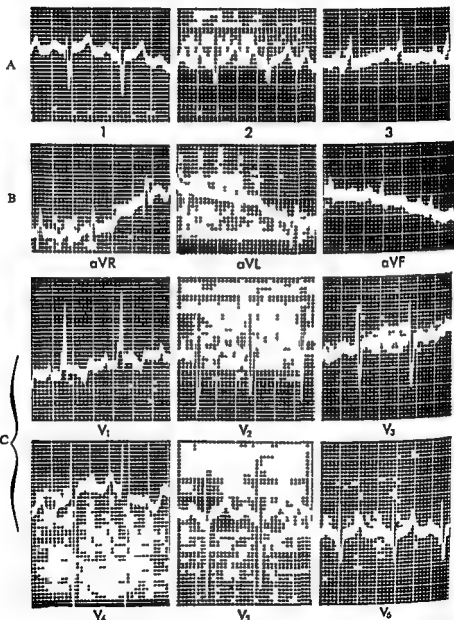


FIG 73 Electrocardiogram in a case of tetralogy of Fallot male age 3 (A) Bipolar limb leads I 2 and 3 (B) unipolar limb leads aVR aVL, and aVF (C) six precordial leads V1 to V6 inclusive Time = 0.04 and 0.20 second amplitude 1 mm = 0.10 mv

procedure consists of the anastomosis of the right or left subclavian artery or in a few instances of the innominate artery to one of the pulmonary arteries thereby bringing blue blood into the lungs for oxygenation largely if not wholly relieving the cyanosis dyspnea weakness polycythemia and clubbing of the fingers in a most dramatic way At the time of writing 1 045 cases of the morbus caeruleus mostly consisting of the tetralogy of Fallot or some variation thereof had been subjected to this operation in Blalock's clinic with a mortality of approximately 18 per cent and a high degree of improvement in the majority of the survivors (Blalock personal communication 1951)

Another technic to aid the victims of the tetralogy of Fallot in a similarly effective way has been introduced by Potts (1946) and consists of a somewhat simpler procedure of side to side anastomosis of aorta and pulmonary artery This operation of Potts has one particular advantage over that of Blalock in that it may be easily carried out in very young infants who might readily expire as a result of the tetralogy of Fallot before they reach the age in which Blalock's anastomotic operation is feasible In both types of operation however it should be noted that a new defect has been introduced by the surgical procedure amounting essentially to a left to right shunt which acts like an arteriovenous communication to increase the work of the heart Taussig (1948) has demonstrated by x ray the increase in heart size that follows the operation even while great improvement is shown by the child Also a continuous murmur resembling that of a patent ductus arteriosus results from the operation Despite this unfavorable point the life of these children has undoubtedly been prolonged though just how much it is still impossible to say The most suitable age for either of these two surgical procedures is probably between 6 and 18 although successful results have been noted earlier and later A more recent surgical procedure has been introduced by Brock (1948) and consists of valvulotomy of the stenosed pulmonary valve the clearing of cyanosis has been noted in a few cases but it is still too early to evaluate this therapy

An important though not very common complication of the tetralogy of Fallot is subacute bacterial endocarditis and therefore the same advice about the therapeutic and prophylactic use of penicillin given for a localized pure ventricular septal defect (see above) should apply here

Finally as stated in the general discussion of congenital heart disease the most important consideration of all is that of the prevention of such a malformation as the tetralogy of Fallot This will doubtless depend in large measure on the protection of the mother from various deleterious influences including virus infections (such as rubella) during the first three months of pregnancy

**The Eisenmenger complex** Another but much rarer variation of the group of ventricular septal defects is that described by Eisenmenger (1897) consisting of this defect overridden by a dextroposed aorta and accompanied by a large right ventricle but with no pulmonary stenosis There were only 7 such cases in Abbott's series of 1 000 in contrast to the 85 patients with the



**tetralogy of Fallot** The symptoms and signs are much the same however in the two conditions though generally less pronounced in the case of the *Eisenmenger complex* which lacks the loud pulmonary systolic murmur and which also shows a normal or even somewhat prominent pulmonary vascular tree on x ray examination

The prognosis with this complex is still not good but in Abbott's series was far better than that of Fallot's tetralogy the mean age being 25 years as contrasted with 12 years On the other hand there is as yet no surgical correction here because a considerable amount of blood does go to the lungs the difficulty consists in the equally large amount of blue blood that enters directly into the systemic circulation

Entire absence of the ventricular septum so that the heart is three chambered (*cor trilobulare biatriatum*) or two chambered (*cor bilobulare*) is rare Surprisingly efficient circulation is possible even with such marked deformity and cases surviving to adult life are on record Although in these cases there is but one ventricle the course of the two blood streams entering it from the atria is often so directed in relation to their inflow and outflow tracts that they may actually mix but relatively little and so not conduce to much of any cyanosis or immediately serious disability of the circulation In Abbott's series of 5 cases with one ventricle and two atria one lived to be 31 years old and the mean age was 6 years There are usually no murmurs or thrills in such cases the cyanosis may be but slight or even absent and the heart may be but little enlarged rendering the diagnosis difficult or impossible The *cor bilobulare* occurred in 9 of the 1 000 cases of Abbott's series, the mean age at death was  $3\frac{1}{4}$  years and the oldest case lived to be only 16

To be distinguished from a congenital interventricular septal defect there occurs rarely a septal defect due to inflammatory ulceration through the upper septum in bacterial endocarditis or following coronary thrombosis Such a lesion is relatively small and usually of little importance as a complication of fatal bacterial endocarditis but it is a factor of added and serious and usually fatal strain in acute myocardial infarction

An interesting and important rare complication of an interventricular septal defect is congenital heart block which has never been found without this structural lesion in itself it is not serious and is apparently compatible with a long life and full activity (Campbell 1943) (see Chapter 34)

**Anomalous papillary muscles and chordae tendineae** In rare hearts there exist unimportant anomalies of the papillary muscles and chordae tendineae for example a papillary muscle found attached to the pulmonary valve in the routine autopsy of a man 69 years old (Collins 1931) and a chorda tendineae extending across the left ventricular cavity from a small papillary muscle of its own to be attached well up on the aortic cusp of the mitral valve in a man of 40 years (Hamilton and Byers 1899) The only importance of such cases lies in the occasional occurrence of unusual snapping intrasytolic sounds or twanging systolic murmurs which may cause undue apprehension

## CONGENITAL MYOCARDIAL DISEASE

The heart muscle may be involved congenitally in a variety of ways. The most common change is that of **hypertrophy**, with or without dilatation secondary to various valvular, septal and vascular defects (for example pulmonary stenosis, large interatrial septal defect, coarctation of aorta). This response to increased work and strain is comparable to that found in acquired valvular heart disease and chronic hypertensia. The muscle fibers are hypertrophied in whatever heart chambers are under particular strain, the right ventricle being by far the most commonly affected compared with the situation a decade or two ago. There are now but few cases of enlargement of this sort that are unexplained; these are grouped as congenital idiopathic hypertrophy. There have been slowly separated from this group three other myocardial changes that are of importance. One consists of **necrosis and fibrosis** associated with hypertrophy, explained on the basis of (1) infection and (2) anoxia and most clearly evident in instances of very faulty anomalous blood supply—for example, when the left coronary artery arises from the pulmonary artery. A second myocardial change is that of the deposition of glycogen in large amounts in vacuoles in the heart muscle in the so-called glycogen storage disease (von Gierke's disease, von Gierke 1929, Pompe 1933); here the enlargement and glycogenization of the heart (Figure 74) are but part of the systemic disease of faulty glycogen metabolism with similar involvement of other organs in the body (especially the liver), fasting hypoglycemia, failure of hyperglycemic reaction, readily elicited ketosis and ketonuria, and early death. The third myocardial condition recently recognized is the dilatation with secondary hypertrophy occurring in very young infants due to excessively fast heart rates in paroxysmal tachycardia (Hubbard 1941) (see Chapter 32).

**Congenital idiopathic hypertrophy of the heart.** One of the least common congenital anomalies of the heart is that which has been called idiopathic hypertrophy. The actual number of cases of congenital idiopathic hypertrophy has been steadily shrinking in recent years because of the special studies which have separated from it the rare cases of glycogen storage disease (von Gierke's disease—see above), myocarditis apparently of infectious origin (Kugel and Stoloff 1933), instances of extensive myocardial necrosis with fibrosis such as that occasioned by a very abnormal coronary blood supply (Bland White and Garland 1933), and cardiac enlargement secondary to formerly unrecognized paroxysmal tachycardia of excessively fast rates in infancy (see above and Chapter 32). There still remain a few unexplained cases.

The heart in congenital hypertrophy (idiopathic or not) is frequently two or three times the normal weight (75 gm for example instead of 25 gm at the age of 4 months) and may also be considerably dilated. In one of our own cases found to be due to glycogen storage disease the heart weight was five

times the normal 175 gm instead of 34 (Figure 74) The cardiac enlargement is easily made out on physical examination and by roentgen ray The heart shadow is uniformly enlarged and roundish in shape prominent to right of the midline as well as to left and without particular dilatation of the atria or great vessels (arteries or veins) The electrocardiogram in uncomplicated cases is not remarkable but with coronary anomalies it may be very abnormal (see end of this chapter)

The male sex is more frequently involved than the female The course is

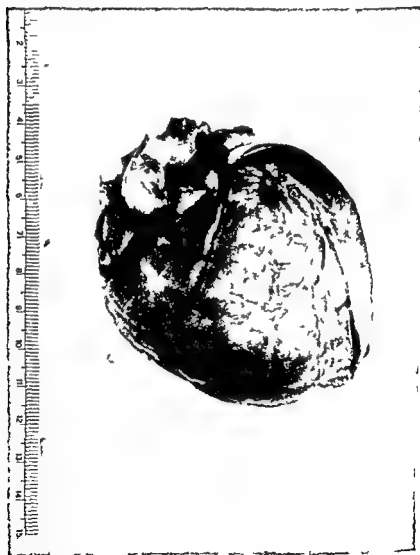


FIG 74 Congenital hypertrophy of the heart due to glycogen storage (von Gierkes) disease This heart of a 7 month-old infant weighed 175 gm instead of the average normal of 34 gm for this age Both ventricles were enlarged but the shape of the heart was not significantly altered from the normal

progressively a downhill one with symptoms and signs of circulatory embarrassment and weakness during the first year of life. Death comes rather suddenly or after increasing dyspnea or systemic venous congestion at about six months to a year or two of age. The oldest patient of Abbott's series of 10 lived only four years.

There is no treatment as yet but further study will doubtless reduce still more the number of cases of congenital idiopathic hypertrophy that are wholly unexplained.

### CONGENITAL ENDOCARDITIS AND VALVULAR DEFECTS

Although acute endocarditis has been noted in the fetus and in the infant at birth it is the late result of such inflammation that is much more frequently seen and which doubtless explains some congenital cardiac defects. Occasionally in cases with pulmonary stenosis, aortic stenosis and other congenital valvular lesions and rarely even in hearts without such lesions the endocardium lining a part or the whole of a heart chamber may be thick and white due to marked fibrosis, the only adequate explanations of which are in most cases a state of chronic anoxia or strain or a fetal endocarditis. The deformed valves in such cases are also thickened and scarred as a rule.

Any heart valve or chamber may show this abnormality but the pulmonary valve and the infundibulum of the right ventricle are much more commonly involved than any other part of the heart quite probably because of the fact that they bear the brunt of the chief cardiac circulatory effort in fetal life, the aortic valve comes a very late second while the mitral and tricuspid valves are affected only rarely. In Abbott's series of 1 000 cases there were 150 cases of pulmonary or infundibular stenosis or atresia, 35 cases of aortic or subaortic stenosis or atresia, 19 cases of tricuspid stenosis or atresia and but 11 cases of mitral stenosis or atresia. Only rarely except in the cases with aortic valve involvement were the valvular defects uncomplicated, the reason for the relatively common uncomplicated occurrence of aortic or subaortic stenosis is probably its late development in the course of intrauterine life. Preponderant valvular regurgitation of congenital origin (involving the tricuspid, pulmonary or aortic valve) is excessively rare as is also multiple valvular disease. Rheumatic valvular disease may infrequently be found as a complication of congenital heart disease.

Pulmonary valve or infundibular stenosis is in the vast majority of cases complicated by septal defects (101 of 110 cases in Abbott's series) most commonly ventricular alone (51 of Abbott's cases) less often both atrial and ventricular (34 of Abbott's cases) and rarely atrial alone (16 of Abbott's cases). Quite often it is associated not only with a ventricular septal defect but also with dextroposition of the aorta and marked right ventricular enlargement to form the tetralogy of Fallot (see page 318). The signs, course and prognosis vary greatly according to the degree of the pulmonary valve or infundibular stenosis and of the associated anomalies particularly the degree

of aortic dextroposition When pulmonary stenosis is a part of the tetralogy of Fallot cyanosis is invariably present with an atrial septal defect cyanosis and finger clubbing are less than in the case of the tetralogy of Fallot but when pulmonary stenosis is independent of septal defects which is a much rarer situation cyanosis is not present until the right heart fails on which occasion stasis in the peripheral circulation is the explanation The characteristic sign of pure pulmonary stenosis is a loud pulmonary systolic murmur with accompanying thrill Congenital pulmonary stenosis has itself in recent years been relieved surgically in a considerable number of cases Valvulotomy was introduced by Brock in 1948 Blalock has followed suit and reports (personal communication 1951) having operated upon 42 cases of valvular pulmonary stenosis with intact ventricular septum with 8 deaths

**Congenital pulmonary regurgitation** is very rare (see Chapter 26 for signs of this valve defect) it may complicate pulmonary or infundibular stenosis **Pulmonary valve atresia** (closure) is always attended by other compensatory anomalies it allows but a very few years of life as a rule, the mean age in Abbott's 40 cases being 4 years and the oldest 30 years

**Aortic valve or subaortic stenosis** is one of the rarer congenital anomalies It doubtless is sometimes wrongly diagnosed as acquired aortic stenosis the signs and course of both are outlined in Chapter 26 The valve is no more frequently involved (11 cases of Abbott's series) than the infundibulum of the left ventricle just below the valve (subaortic stenosis) (12 cases of Abbott's series) **Congenital aortic regurgitation** of any high degree has not yet been reported so far as I am aware in slight degree it may complicate aortic stenosis or the dilatation of the aorta encountered in the tetralogy of Fallot **Aortic valve atresia** is incompatible with life for more than a few months at best (maximal age of the 12 cases of Abbott's series 15 weeks mean age 8 weeks) there must of necessity be a compensatory patency of the ductus arteriosus

**Mitral and tricuspid valve stenosis and atresia** are rare anomalies almost always attended by compensatory septal defects The average duration of life in cases with these anomalies is short The commonest of these defects is tricuspid atresia of which there were 16 examples in Abbott's series the oldest survived to the age of 56 years There were 3 cases of tricuspid stenosis (the oldest 28 years of age) 6 cases of mitral stenosis (oldest 27 years), and 5 of mitral atresia (oldest 31½ years) Clinical recognition of defective development of the right ventricle associated with tricuspid atresia or hypoplasia has been established (Taussig 1936) the diagnostic criteria consist of cyanosis in infancy much diminished roentgen ray shadows of right ventricle and pulmonary artery left axis deviation by electrocardiogram (Figure 75) and absence of murmurs It is to be treated surgically by Blalock's or by Potts operation as in the case of the tetralogy of Fallot (q.v. for details) In very young infants Potts operation is more suitable than Blalock's and may be lifesaving prior to the time of the arrival at the age when the more complicated procedure is feasible (Gasul et al 1949) **Tricuspid regurgitation**

has been described and is due to displacement of the attachment of the cusps of the valve (Ebstein 1866 Yater and Shapiro 1937)

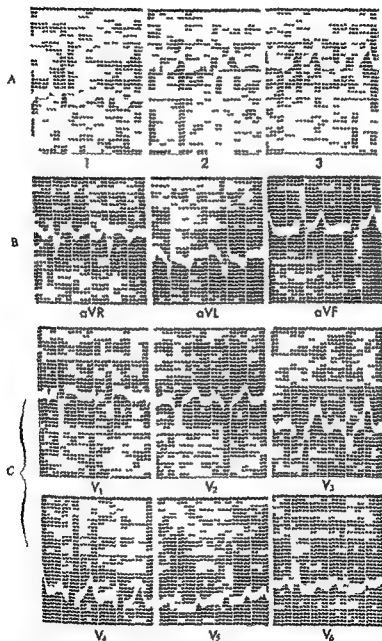


FIG 75 Electrocardiogram in a case of tricuspid atresia male age 7 years (A) Bipolar limb leads I 2 and 3 (B) unipolar limb leads aVR aVL and aVF (C) six precordial leads V<sub>1</sub> to V<sub>6</sub> inclusive Time = 0.04 and 0.20 second amplitude 1 mm = 0.10 mv

## CONGENITAL PERICARDIAL DEFECTS

There are several types of pericardial abnormality of congenital origin all rare. These include absence or defects of the parietal pericardium (30 cases in Abbott's series), and diverticulum or hernia (6 cases in Abbott's series).

The parietal pericardium may be entirely absent so that the heart lies in the left pleural cavity along with the left lung or it may be defective in part most commonly over the region of the pulmonary artery. In the case of ectopia cordis there may or may not be a pericardial sac; the cases with better prognosis have such a sac. When the parietal pericardium is absent the heart is usually freely movable both on respiratory movements and with changes of body position. Physical examination and especially roentgen ray study may reveal this extreme mobility. The clinical significance of absence or defect of the parietal pericardium is practically nil in itself, normal duration and activity of life being possible without any cardiac strain or circulatory embarrassment. Two complications may arise, however. One is due to close contact of heart with left lung and pleura so that disease of the latter may seriously affect the former and vice versa, there no longer being protection by an intervening cavity. Pleurisy with effusion, empyema and pneumonia have been reported as fatal illnesses in the cases on record with absence or deficiency of pericardium. Another complication of importance that has been reported, resulting in pain or even death, is sudden kinking of the great vessels due to the fact that the heart is so freely movable.

The other two congenital anomalies of the pericardium, diverticulum and absence of attachment, are very rare and of no clinical importance when they do occur except that occlusion of the orifice and consequently distension of the cavity of a pericardial diverticulum may interfere somewhat with the heart's action.

## CONGENITAL ANOMALIES OF THE AORTA

Congenital aortic anomalies found mostly in young persons are due to maldevelopment in fetal life or at birth and include hypoplasia, coarctation, right aortic arch, double aortic arch, aneurysms and transposition of the aorta and pulmonary artery as well as septal defects between aorta and pulmonary artery, right ventricle or auricle and patency of the ductus arteriosus.

## Aortic Hypoplasia

Hypoplasia (ὑπο under and πλάσις formation) or small caliber of the aorta throughout its course is one of the commonest of the congenital aortic anomalies but in high degree it is relatively rare and it is then usually associated with other congenital cardiovascular defects. In Abbott's series it was found in

77 cases 75 of which showed other defects the commonest associated abnormality was an atrial septal defect With such a defect there is a combination of a very large pulmonary artery and a small aorta due to the overloading of the pulmonary circulation and the underloading of the systemic There is general hypoplasia of the arterial system when there is much aortic hypoplasia with a tendency to pallor slow and incomplete growth and retardation of sexual development Small heart size and large heart size have both been reported in this condition and heart failure in youth is said to have resulted from the strain due perhaps in part to a high degree of aortic narrowness but more probably to complicating congenital defects in the heart itself

### Coarctation of the Aorta

Coarctation (*co-* together and *arctare* to press or make tight) of the aorta is a localized narrowing of the aorta of greater or lesser degree in the vicinity of the insertion of the ductus arteriosus which sometimes remains patent Morgagni (1761) was the first to record its discovery at autopsy It is a fairly common abnormality having been noted in 142 of Abbott's series of 1000 cases of congenital cardiovascular defects in 79 of which it was the primary lesion and in the other 63 a complication of other anomalies slight grades are likely to be missed even on postmortem examination and are of no clinical importance

**Etiology and pathology** There have been described two chief types of aortic coarctation called the infantile and the adult but there is not always a sharp separation between them The first (or infantile) a rare type (37 cases in Abbott's series only 9 of which were primary) consists of narrowing of the whole isthmus that is that part of the aorta between the left subclavian artery and the ductus arteriosus sometimes the proximal arch itself is also involved In fetal life the isthmus has little function since blood enters the descending aorta largely through the ductus arteriosus therefore it quite naturally remains hypoplastic This fetal condition may persist for a few weeks or months after birth to a greater or lesser degree but rarely is it found in adult life In extreme cases it may be represented simply by a fibrous cord in the circulation to the lower part of the body being taken care of wholly in such cases by the patent ductus arteriosus which thus supplies only venous blood to the abdominal viscera and legs with resulting disability The infantile type is serious usually associated with other important anomalies and had been thought to be incompatible with long life there having been a maximum of 9 months and a mean of 8 hours in Abbott's series of 31 primary cases However recently Johnson and Kirby (1948) have reported using in three patients aged 13 17 and 20 years respectively the left subclavian artery to bridge the long gap of the coarcted aorta of the infantile type with success in one case partial benefit in a second and failure in a third

The second (or adult) type of aortic coarctation consists of localized constriction of the aorta in or most often just below the insertion of the ductus



arteriosus and rarely above that point (Figure 76) It is much more common than the infantile type and less serious in Abbott's series there were 105 cases in only 35 of which the condition complicated other defects It is probably always a prenatal condition developing in the fetus In only a few of the cases does the ductus arteriosus remain patent There may be other congenital cardiovascular anomalies especially when the coarctation is extreme

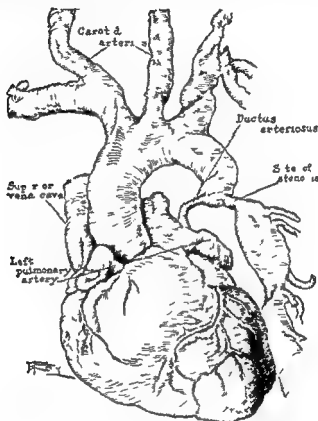


FIG 76 Coarctation of the aorta (adult type) just below the ligamentum arteriosum (Case of Dr W B Shelden) (Blackford Coarctation of the Aorta *Arch Int Med* May 1928)

but frequently the condition is uncomplicated The most common associated anomaly is the bicuspid aortic valve either congenital or acquired in origin found by Abbott in 50 out of 183 collected cases (Abbott 1928) and in 47 per cent of 104 additional autopsied cases reported by Reifenshein et al. in 1947 All grades of narrowing of the aorta occur from that which is so slight that it can scarcely be seen on careful postmortem scrutiny up to complete local aortic obliteration Coarctation has been noted more often in the male than in the female the adult type being three to five times more frequent in the male sex why this is so is not known In a recent series of 96 cases reported at the Mayo Clinic (Christensen and Hines 1948) there were 76

males and 20 females this ratio is characteristic of other series. It has also been found in more than one member of a certain family (Walker 1934).

The result of pronounced coarctation of the aorta of the adult type on the circulation is of much interest. The aorta is usually considerably dilated above the constriction (sometimes with an aneurysm) and often but not always narrowed below. A collateral circulation is developed at times in high degree blood being carried to the lower part of the body by widely dilated tortuous internal mammary, scapular and intercostal arteries. The heart becomes enlarged in most cases and sometimes is markedly hypertrophied and dilated. Hypertension accompanying the coarctation is responsible for this cardiac hypertrophy as a rule but on occasion acquired valvular disease which is a not infrequent complication may be an additional factor. The arterioles in the muscle and skin of the arms in young subjects are normal and indistinguishable from those in the legs (Graybiel, Allen and White 1935). The hypertension usually found in persons with aortic coarctation need not be wholly ascribed to the defect directly but may be due in part at least to a secondary effect namely the diminution of the renal blood flow below the constriction which in turn causes a generalized vasoconstriction reflexly or through the production of the chemical mediator called hypertensin or angiotonin (see Chapter 19) (Steele and Cohn 1938) when the collateral circulation is very richly developed the blood pressure may be perfectly normal the renal circulation also then being adequate. The early hypertension in cases of aortic coarctation is sometimes attended by congenital intracranial aneurysms (as in the circle of Willis). Also unusual blood supply to the teeth has been reported in coarctation of the aorta.

**Symptoms and signs.** There are no particular symptoms of the adult type of coarctation of the aorta and often no signs or so slight that the anomaly escapes notice during life. With high grades of coarctation however there are a number of important signs. (1) inequality of blood pressure and of pulse fullness and form between the upper and lower extremities the brachial systolic pressure often being much elevated (even to 200 mm of mercury or more) while the femoral blood pressure is low (100 mm or less as a rule) and the femoral pulse is small although the diastolic pressure levels may be much the same. (2) evidence of compensatory collateral circulation between the upper and lower parts of the body the internal mammary, intercostal, scapular and deep epigastric arteries being much dilated tortuous and in the case of the first three groups of vessels easily felt and sometimes visibly pulsating. (3) long systolic murmurs transmitted from the aortic coarctation itself heard not only over the precordium and back but especially down the spine where it may be heard to extend into diastole and also along the course of the dilated tortuous anastomotic vessels sometimes accompanied by palpable thrills. (4) decrease or absence of the shadow of the aortic knob by roentgen ray frequently with dilatation of the ascending aorta and first part of the arch. (5) roentgen ray evidence of well marked notching of the ribs due to the dilated tortuous intercostal arteries (Figure 77) and (6) enlargement of

the heart and sometimes signs of failure due in part to frequent complicating heart lesions (especially acquired valvular disease) but in large part to the hypertension associated with the stenosis of the aorta. It should be reiterated that the brachial systolic pressure is not always high in cases of coarctation of the aorta but there is almost always a greater blood pressure in arms than in legs. Retrograde arterial or direct aortic Diodrast injections can helpfully outline the roentgen ray shadow of the coarcted aorta and of some of the collateral circulation for confirmation of the diagnosis and especially as guidance for the surgeon.



FIG 77 X ray photograph of a 19 year-old boy with coarctation of the aorta demonstrating notching of the ribs and absence of aortic knob. (Blood pressure in the arms 175/110 blood pressure in the legs 135/100)

**Course and prognosis Complications** The course and prognosis of coarctation of the aorta vary enormously depending chiefly on the degree of narrowing of the aorta and the extent of the collateral circulation but even when slight the condition is important because of the possibility of local infection in the form of subacute bacterial aortitis or endocarditis of a bicuspid aortic valve. Marked coarctation is often a serious anomaly which may kill in youth by one of four complications heart failure rupture of the aorta itself apo-

plexus due to cerebral hemorrhage or thrombosis and bacterial infection invading the area of coarctation or the aortic valve. On the other hand it is compatible with long life as in the case of a 92 year old man with completely closed aorta (Abbott 1928).

Of a series of 200 cases of the adult type collected by Abbott (1928) the average age at death was close to 32 years with extremes of 3 and 92 years. 60 died of congestive heart failure, 40 of sudden heart (2) or aortic (38) rupture, 26 of cerebral complications and 14 of bacterial endarteritis. Of a more recent series of 104 autopsied cases (Reifenstein et al 1947) 23 per cent died of rupture of the aorta, 22 per cent of bacterial invasion, 18 per cent of congestive heart failure, 11 per cent of intracranial lesions and 26 per cent of incidental causes.

Between 5 and 10 per cent of cases with coarctation of the aorta have an associated patency of the ductus arteriosus. For example 8 of 140 cases surgically treated by Gross (personal communication 1950), 10 per cent of a series at the Mayo Clinic (Taylor et al 1950) and 10 per cent of Abbott's cases.

**Treatment** In the last edition of this book it was stated that there was no special therapy for congenital coarctation of the aorta but that the subject should be protected as much as possible from physical strain and infections. In the intervening years there has occurred a great advance due to the introduction independently by Crafoord (1945) and Gross (1945) of surgical correction of the defect by excision of the area of coarctation and end to end anastomosis of the cut ends of the aorta in children and young adults where the narrowed portion is long the left subclavian artery or a vascular graft can be used to bridge the gap. Postoperatively the blood pressures in arms and legs equalize at normal levels. Of the first 100 cases operated upon by Gross (1950) 11 died and they were for the most part early cases of the others 71 were completely relieved, 8 others satisfactorily improved, one unchanged and 9 explored only (because of findings contra-indicating operations on the aorta itself). Blalock has written to me (February 1951) of having operated upon 103 cases of coarctation of the aorta with 11 deaths.

**Differential diagnosis** There is one condition with which coarctation of the aorta is commonly confused and that is hyperpiesia (essential hypertension). The differentiation is however easy if one has in mind the possibility of the congenital defect especially in a child or young adult the difference between the blood pressures of arms and legs, the systolic or continuous murmur transmitted down the upper spine, the palpable intercostal artery pulsations and the notching of the ribs seen by roentgen ray at once lead to the correct diagnosis.

#### Other Rare Congenital Aortic Anomalies

These are (1) localized weakness of the wall resulting in aneurysms usually small, (2) transposition of the aorta and pulmonary artery so that the former

arises from the right ventricle and the latter from the left as the result of reversed torsion of the common arterial trunk in the course of fetal development (3) a right sided instead of a normal left sided aortic arch and (4) a double aortic arch due to persistence of the right hand side of the fourth primitive arch

**Congenital defects in the aortic wall** Congenital defects in the aortic wall with thinning and even outpocketing (aneurysm) are very rare and small. They are an incidental finding at postmortem examination and are of no clinical importance. The medial necrosis responsible for dissecting aneurysms does not belong here

**Transposition of the great arteries** Transposition of the great arteries is an infrequent anomaly found much more often in the male sex than in the female in the ratio of about 4 to 1. It is incompatible with survival for more than a few hours or days after birth unless there is a septal defect which allows some venous blood to reach the lungs. Such defect usually consists of a patent foramen ovale. In some cases there is also an interventricular septal defect or a patent ductus arteriosus. When the ventricular septum is defective life may last for years but the handicap is a serious one and death occurs almost always before adult age is reached and is due to heart failure or complicating infections. In Abbott's series of 1 000 cases of congenital cardiovascular defects there were 74 cases of complete transposition of the aorta and pulmonary artery in 49 of which it was the primary defect. Of these 49 cases, 32 had a closed ventricular septum with longest survival to 11 years while 17 had a ventricular septal defect with longest survival to 16 years.

Cyanosis is an almost invariable sign of complete transposition of aorta and pulmonary artery except in early infancy when the cyanosis tends to be absent or less marked than later as is the case also in some other congenital cardiac anomalies. The cyanosis sometimes becomes very marked and it is then accompanied by definite clubbing of the fingers. The heart is enlarged particularly the right ventricle and the electrocardiogram shows abnormal right axis deviation. Roentgenologic study may show little except the cardiac enlargement but there may be some suggestion of the anomaly of the great arteries especially in the oblique views. There may or may not be heart murmurs and thrills dependent on the presence of other anomalies such as patency of the ductus arteriosus. uncomplicated transposition of the great arteries should not cause murmurs.

The antemortem diagnosis of complete transposition of the aorta and pulmonary artery is extremely difficult but Taussig (1938) has pointed out the combination of four characteristic features (1) persistent cyanosis (2) cardiac enlargement especially of the right ventricle (3) a narrow aortic shadow in the anteroposterior roentgenogram and (4) an increase in the width of the roentgenographic shadow cast by the great vessels when the patient is placed in the left anterior oblique position.

A hopeful development in these very serious cases has taken place since the last edition of this book was published through the introduction by

Blalock of the production of an atrial septal defect and sometimes in addition the anastomotic operation which he has used in cases of the tetralogy of Fallot namely joining subclavian and pulmonary arteries on the right. He has operated upon 62 cases with 38 deaths the best results have been in patients with pulmonic stenosis as well as transposition and in patients with the Taussig Bing syndrome (Blalock personal communication 1951).

**Corrected transposition of the great vessels** There is a condition called corrected transposition of the great vessels in which the aorta and pulmonary artery although in abnormal position regarding each other arise nevertheless from the correct ventricles. Such an anomaly in slight degree is of little or no clinical importance since the circulation is maintained practically in a normal manner and the condition may not be very obvious even at postmortem examination. When of marked degree however it is associated with other anomalies such as interventricular septal defects and life does not last beyond early adult years there were but 6 cases in Abbott's series 4 of which were primary in type with longest survival to 24 years.

Finally a third type of transposition occurs called partial transposition in which both aorta and pulmonary artery arise from the same ventricle. As in the case of complete transposition with septal defect there is frequently cyanosis. Life is usually short in this condition averaging  $4\frac{1}{2}$  years in 16 primary cases collected by Abbott.

**Right or double arch Vascular ring** Anomalies of the aortic arch consisting of a right or double arch are rare and for the most part unimportant except that there tends to be more or less compression of esophagus and trachea between the aorta and ductus arteriosus in the case of the right aortic arch and between the two sides of the arch when it is double. In some cases this obstruction is an important complication and rarely it may be serious with *dysphagia* (called *lusoria* from the Latin meaning deceitful) esophageal dilatation and ulceration tracheal stenosis and asphyxia. With obstruction of high degree and the diagnosis of right or double aortic arch established surgical cure by transecting the constricting vascular ring has been effected by Gross (1945) since the last edition of this book was published. *Dysphagia lusoria* has also been noted in cases with certain other anomalies of the great arteries for example when the right subclavian comes off the descending thoracic aorta instead of the innominate artery. The diagnosis must rest in the main at least on roentgen ray evidence of reversed position of the aortic arch or of its double character and on abnormal deviation or obstruction of the trachea and also of the esophagus as studied fluoroscopically during the ingestion of barium (Figure 78).

In Abbott's series there were but 5 cases of double aortic arch the oldest surviving to 37 years and 35 cases of right aortic arch 14 classified as primary with the oldest case 61 years females outnumbered males (8 to 5) in a small series of 13 cases of these two anomalies Abbott recorded 7 cases in her total collection of 1 000 who showed the right subclavian artery arising from the descending aorta and 8 cases with left subclavian artery arising

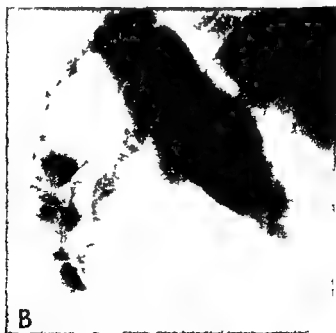


FIG 78 Roentgenograms showing a right aortic arch displacing trachea and barium filled esophagus forward and to the left (A) Anteroposterior view (B) right anterior oblique view (kindness of Dr Hugo Roesler Temple University Philadelphia)





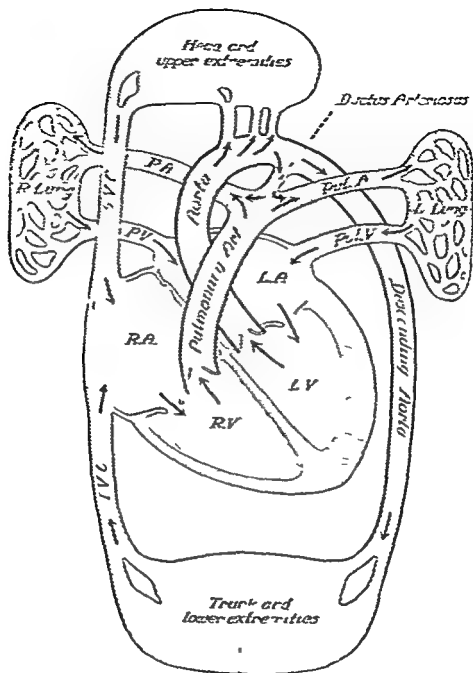


FIG. 79. Diagram of the human circulatory system. (Adapted from D. H. Lewis, Textbook of Human Physiology, Baltimore, and The Commonwealth Fund, New York City.)

from either the ductus arteriosus or the pulmonary artery in the former group one of 5 cases lived to be 44 the oldest age noted while the one case of the latter whose age at death was noted was only 5 years old

### COMMUNICATIONS BETWEEN THE AORTA AND PULMONARY ARTERY

There are four types of congenital communication between the aorta on the one hand and pulmonary artery right ventricle or right atrium on the other hand They are first and most common patency of the ductus arteriosus second rare cases of a persistent truncus arteriosus without separation into aorta and pulmonary artery third very rare instances of communication between the aorta and pulmonary artery by arterial septal defect and fourth very rare cases of communication between aorta and right ventricle or right atrium by septal defects The possible rupture of the aorta into right ventricle or right atrium in bacterial endocarditis and endarteritis or into the pulmonary artery in syphilitic aortitis is discussed elsewhere (see Chapters 15 and 28 respectively)

#### Patency of the Ductus Arteriosus

The ductus arteriosus (also called *ductus Botalli* Botallo 1530) which normally in the fetus diverts most of the blood from the pulmonary artery into the aorta should cease to function soon after birth it should be converted within a few weeks into a fibrous cord the *ligamentum arteriosum* Its obliteration may however be delayed for some months or it may persist as a patent arterial canal throughout life Its patency may be regarded as a congenital anomaly if it is found later than three months after birth (Figure 79) It is one of the commonest of all congenital cardiovascular defects ranking third in incidence (242 cases 92 as the primary and 150 as a complicating defect) after interatrial and interventricular septal defects respectively in Abbott's series of 1 000 cases Because of its curability now in childhood physicians in general have become much more familiar with its diagnosis For the anatomic position of the ductus arteriosus see Figure 76 page 330

**Etiology Cause** The cause of persistent patency of the ductus arteriosus is not always clear Frequently it appears to be a compensatory condition in the presence of some serious cardiovascular defect like infantile coarctation of the aorta or transposition of the great arterial trunks in other cases it is due to an unexplained arrest of development

**Age** Beginning at birth it may last through a long life It has been noted most often in children and young adults the mean age at death of 92 cases of simple patency in Abbott's series being 24 years It is frequently found in old people the oldest autopsied cases on record being 66 years (Josefson 1897 White 1928) a man with this condition still in good health at 75 years has been followed by the author for 27 years while another case reported by Walker and Ellis in 1941 then in good health at the age of 73 died suddenly

at the age of 78 five years later while mowing his lawn (there was no autopsy—personal communication)

**Sex** Patency of the ductus arteriosus has been found more often in the female sex in the ratio of 2 to 1 (55 to 29 in Abbott's series of 92 cases of simple patency in which the sex was stated and 333 to 145 in Gross' series of 478 cases—Gross' personal communication 1951)

**Pathology** The patency of the ductus arteriosus varies very much in degree, from that of a fine canal barely admitting a small probe or bristle to that of large caliber easily admitting pencil or finger. It may be very short so that there is hardly more than a direct opening between contiguous aorta and pulmonary artery or it may be several centimeters long usually it is  $\frac{1}{2}$  to 2 cm long. It may be cylindrical in shape funnel shaped or conical with wider end at the aorta or it may be dilated to form a kind of aneurysm. In patency of the ductus arteriosus of long duration or of marked degree especially in the combination of these conditions the pulmonary artery is dilated and both ventricles are enlarged with hypertrophy and dilatation the blood flow from aorta to pulmonary artery increasing the work of both ventricles in such cases the right ventricle has to overcome the pressure directed against its own blood stream and the increased blood flow through the lungs and the left ventricle has to increase its output to make up for the diversion of a considerable amount of blood from the systemic circulation. It has been estimated that as much as 25 to 75 per cent of the blood pumped out by the left ventricle may be diverted into the pulmonary circulation via a patent ductus arteriosus. Atheroma with calcification is commonly found in the patent ductus arteriosus especially at its mouth in the aorta and often also about its orifice in the pulmonary artery. Very rarely spontaneous thrombosis may obliterate the ductus.

The ratio of complicated to uncomplicated patency of the ductus arteriosus is about 2 to 1. In Abbott's series of 150 complicated cases it was found associated with coarctation of the aorta 13 times (6 out of 70 cases of the adult type 7 out of 8 of the infantile type) with complete transposition of the great arterial trunks in 33 cases with pulmonary atresia 28 times with pulmonary stenosis 12 times and with tricuspid atresia 6 times.

The ductus arteriosus may take an anomalous course or even be entirely absent. Rarely it gives off the left subclavian artery.

**Symptoms** There are no symptoms of patency of the ductus arteriosus itself except in a rare patient who is conscious of the harsh murmur and thrill caused by the rush of blood through the ductus and in occasional cases where the ductus is so large that there is retardation of growth or when dyspnea develops because the heart fails as it would from aortic regurgitation or a large arterio-venous communication.

**Signs** Usually pathognomonic evidence of the condition is present. There are two important signs one diagnostic the other suggestive when both are present the diagnosis of patent ductus arteriosus may be regarded as certain.

The first sign is a continuous murmur usually loud with systolic accentuation maximal over and often limited to the region of the pulmonary artery.

at the second rib and intercostal space just to the left of the sternum and not so loud in the neck and generally attended by a palpable thrill (in the absence of evidence of rupture of aorta into pulmonary artery) This murmur has been variously described as resembling the sound of a humming top of a mill wheel or other machinery of a train in a tunnel or of rolling thunder It is almost invariably harsh rarely blowing In cases with a right aortic arch the continuous murmur is heard over the patent ductus at the right of the upper sternum instead of at the left In some cases with wide ductus patency and a dilated left ventricle there may also be heard a mitral muddiastolic murmur simulating mitral stenosis

The second important sign is roentgenologic consisting of unusual prominence of the heart shadow in the region of and just above the pulmonary artery (Figure 80) without increase in the size of the left atrium pointing to mitral stenosis and without cyanosis which might result from pulmonary endarteritis obliterans This abnormal bulging of the left upper border of the heart shadow is more pronounced in some cases of patency of the ductus



FIG 80 Roentgenogram of thorax in case of congenital patency of the ductus arteriosus Note the bulge in the region of the pulmonary artery JW male now 75 years with characteristic machinery murmur This film was taken 13 years ago but there has been no change since

arteriosus than in any other condition except that of interatrial septal defect which presents much larger shadows of both pulmonary artery and lung hilus shadows without a continuous murmur. If there is but a narrow lumen through the patent ductus the roentgen ray sign may be minimal or absent while the typical murmur may be marked. If on the other hand there is a very wide lumen with much blood flow the roentgen ray sign is marked and the murmur minimal or absent. In infants and rarely in young children the murmur may be absent or but slight and only systolic in time during the first few years of life. In adults it is almost invariably present as a typical continuous murmur, but there are rare exceptions with systolic murmur alone.

Other signs are those associated with cardiac enlargement which is found in some of the cases. Various complications and in a few cases a full pulse pressure due to low diastolic pressure when the patency is so wide that there is considerable aortic regurgitation into the pulmonary artery in diastole. A wide pulse pressure in patency of the ductus arteriosus is however not the rule and a water hammer pulse is very rare.

**Course, complications, and prognosis.** Patency of the ductus arteriosus may be a condition compensating for the presence of some serious congenital defect like transposition of the great arterial trunks thereby helping together with septal defects to prolong life, in such cases however life is short at best lasting only a few years. Uncomplicated patency may or may not be an important burden for the heart. If it is of large caliber it is a serious condition leading to considerable cardiac enlargement and failure in youth. If it is of small caliber it may limit neither activity nor duration of life, death in old age being caused by some noncardiac disease. The oldest cases proved at autopsy were 66 years of age at death but two other cases have been known to have reached the middle or upper seventies (see above under etiology, etc.). Always however patency of the ductus arteriosus is something of a menace because of the likelihood of invasion by subacute bacterial (*Streptococcus viridans*) endarteritis which used to end fatally in the course of months just as did subacute bacterial endocarditis with which it may be associated. In Abbott's series of 92 primary cases of ductus arteriosus patency death was ascribed to subacute bacterial endarteritis in nearly one quarter while Gelfman and Levine (1942) found 4 such cases (29 per cent) among 14 patients with patency of the ductus.

Rupture of a dilated pulmonary artery due to ductus arteriosus patency has been observed as a rare complication. Also paradoxical embolism has been noted, thrombi from the left atrium or vegetations from the mitral or aortic valves entering the pulmonary circulation by way of the patent ductus arteriosus. A reversal of current may sometimes occur generally as a terminal event when the blood pressure in the pulmonary circulation for any reason exceeds that in the systemic circuit. In infants there may be transient attacks of dyspnea and cyanosis when the pulmonary pressure is raised by crying and by holding the breath during nursing. Of 92 cases of Abbott's series death in 40 was sudden or due to myocardial failure in 21 to bacterial endarteritis or

endocarditis in 3 to a cerebral lesion in 3 to bronchopneumonia and in the remainder unstated

**Treatment** A decade ago there was finally introduced what had been prophesied namely specific treatment for patency of the ductus arteriosus. Surgical interference to ligate the ductus was successfully accomplished and a new and dramatic era in the treatment of congenital heart disease began (Gross and Hubbard 1939). The operation has now been carried out in many hundreds of cases by various surgeons throughout this country and abroad with very low mortality and with excellent results. Transection rather than simple ligation is now recommended by Gross (1947) although excellent results have been obtained by ligation. Surgical correction is now definitely indicated in all children and young adults to relieve the heart of strain and to avert the dangerous and common complication of subacute bacterial (*Streptococcus viridans*) endarteritis but it must be recognized that there are some patients in whom the condition is inoperable (Shapiro and Keys 1943) and that there still exists in any case a definite operative risk. Surgery has also been proved (Touffo and Vesell 1940 and 1942 Bourne 1941) to have a place with or without chemotherapy in the cure of subacute bacterial infection of the ductus and pulmonary artery. It is striking to note the disappearance of murmur and thrill after ligation of the ductus and in those cases with cardiac enlargement and increased pulse pressure even of such signs too and on occasion even of a mitral middiastolic murmur due to left ventricular dilatation. In those cases not operated upon protection against infection and exhaustion is advisable. The routine use of penicillin to ward off bacterial endarteritis during infections and surgical procedures including tooth extraction is to be recommended as in the case of a ventricular septal defect (q v).

**Differential diagnosis** In infants the condition may be undiagnosable. In adults the distinctive murmur is almost invariably present this murmur must be differentiated from the venous hum sometimes heard in the neck especially on the right side in children which hum may be transmitted downward over the upper chest but is quickly obliterated by compression of the neck veins and it must also be distinguished from the murmur of an arteriovenous aneurysm uncommon in the upper chest and usually located on the right side. A rare condition accompanied by the continuous murmur characteristic of patency of the ductus arteriosus both in position and in character is rupture of an aortic aneurysm into the pulmonary artery the differentiation can be made by analysis of the clinical course. The roentgen ray sign of marked prominence of the pulmonary artery though helpful is not pathognomonic of patency of the ductus arteriosus for mitral stenosis pulmonary fibrosis or endarteritis obliterans and interatrial septal defects must be excluded before a sure diagnosis is justifiable.

### Other Communications Between Aorta and Pulmonary Artery

The other communications between aorta and pulmonary artery are much less common. The first is the serious condition of a common arterial trunk (*truncus arteriosus communis*) with its accompanying intense cyanosis, absence of lung hilar shadows, and short life (averaging but 4 years in 21 cases analyzed by Abbott). A second is an opening between these two vessels above the valves, usually small and not so important (in Abbott's series 10 cases with survival to 48 years in the oldest). The third is a defect between the right sinus of Valsalva and the right ventricle with or without an associated slight interventricular septal defect just below the valve or between the posterior sinus and the right atrium. The defect may exist from birth or there may be in early life simply a thinned wall or aneurysm which may rupture fatally into the right ventricle (Hirschboeck, 1942). There are no symptoms caused by these anomalies. The signs in cases of the second and third categories above in which there are definite though small openings are much like those of patency of the ductus arteriosus with loud continuous murmur lower in position and very near the ear. The cardiac strain results in enlargement but the particular danger appears to lie in a serious complication of bacterial infection of the walls of the defect.

### CONGENITAL ANOMALIES OF THE VEINS

Congenital anomalies of the veins are of little or no clinical importance. They are frequent in the case of the small veins and rare in the case of the venae cavae and chief pulmonary veins. The commonest defect of the great systemic veins is persistence of the left superior vena cava emptying into the right atrium by way of the coronary sinus (36 cases in Abbott's series, 27 of which complicated other defects); associated with it in most cases is the usual (right) superior vena cava, but sometimes it is alone and receives blood from the right side by way of an extensively developed vena azygos major. In rare cases the single superior vena cava or the inferior vena cava is displaced to the left and opens into both atria at the point of a septal defect. Rarely also the left hepatic vein persists and empties into the anomalous left superior vena cava which thus represents the persistent left sinus venosus of the embryo. Many different variations are possible in the case of the pulmonary veins (58 cases total in Abbott's series, all but 4 complicating other defects). The two right or two left veins sometimes coalesce before entering the left atrium or one or more of the pulmonary veins may empty into the right side of the heart into the persistent left superior vena cava into the normal superior vena cava or into the innominate or hepatic vein. Almost always there are cardiac anomalies associated with congenital abnormalities of the venae cavae and with the more important abnormalities of the pulmonary veins. Symptoms, signs, course and prognosis depend on these other anomalies and not on the venous defects. The diagnosis of uncomplicated congenital defects of the great veins has now become possible in some cases by

means of cardiac catheterization and by detailed x ray studies including angio cardiography

# CONGENITAL ANOMALIES OF THE CORONARY VESSELS

Most anomalies of the coronary arteries and veins are of no clinical importance and are simply postmortem curiosities. These include extra coronary mouths (for example the left circumflex coronary artery may arise directly from the aorta) one coronary mouth giving rise to both right and left coronary arteries and unusual course and branching of the vessels. Rarely however a serious anomaly occurs: this consists most frequently of the origin of the left coronary artery from the pulmonary artery which results in cardiac enlargement with hypertrophy and dilatation of the left ventricle myocardial necrosis and fibrosis and early death in the course of the first few months of life. One notable case was of a baby boy dying at the age of four months who suffered from attacks during life which closely resembled angina pectoris and showed an electrocardiogram with inverted (coronary) T waves in Leads 1 and 2 (Bland White and Garland 1933). Other cases have since been reported one diagnosed antemortem (Eidlow and Mackenzie 1946).

The most common important anomaly of the coronary veins is the persistence of the left superior vena cava (mentioned above) which takes the place of the coronary sinus: this anomaly has however no clinical significance. A very rare anomaly is the drainage of the coronary sinus into the left auricle.

## BIBLIOGRAPHY

### CONGENITAL CARDIOVASCULAR DEFECTS

SEE ALSO GENERAL REFERENCES FOLLOWING CHAPTER 2 AND REFERENCES IN CHAPTERS 7 AND 11

#### General

- Abbott M E *Atlas of Congenital Cardiac Disease* American Heart Association New York 1936
- Abbott M E and Dawson W T "The Clinical Classification of Congenital Cardiac Disease with Remarks upon Its Pathological Anatomy, Diagnosis and Treatment" *Internat Clin* 1924 IV 156
- Abbott M E and Weiss E "The Diagnosis of Congenital Cardiac Disease" *Blumer's Bedside Diagnosis* Philadelphia, 1928
- Baillie M *The Morbid Anatomy of Some of the Most Important Parts of the Human Body* J Johnson and G Nicol London 2nd ed 1797 (1st ed 1793) Chapters 1 and 2
- Farber S and Hubbard J "Fetal Endomyocarditis: Intra Uterine Infection as Cause of Congenital Cardiac Anomalies" *Am J M Sc* 1933 CLXXXVI 705
- Farre J R *Pathological Researches: Essay I On Malformations of the Human Heart* Longman Hurst Rees Orme Brown London 1814
- Fletcher P H and Southworth H "Arachnodactyly and Its Medical Complications" *Arch Int Med* 1938 LXI 693
- Gelfman R and Levine S A "Incidence of Acute and Subacute Bacterial Endocarditis in Congenital Heart Disease" *Am J M Sc* 1942 CCIV 324
- Guitrac E *Observations et Recherches sur la Cyanose ou Maladie Bleue* J Pinard Paris 1824



- Gregg N M "Congenital Cataract Following German Measles in the Mother" *Tr Ophth Soc Australia* 1941 III 35
- Harris J S and Farber S "Transposition of the Great Cardiac Vessels with Special Reference to the Phylogenetic Theory of Spitzer" *Arch Path* 1939 XXVIII 477
- Keith A "The Hunterian Lectures on Malformations of the Heart" *Lancet* 1909 II 359 433 and 519
- Laubry C and Pezzi C *Traite des Maladies Congenitales du Coeur* J B Baillière et Fils Paris 1921
- Levinson S A "Congenital Heart Disease as Cause of Sudden Unexpected Death in Children Under One Year of Age" *Am J Clin Path* 1941 XI 741
- McLean S A "Cardiac Development Defect with Return to Normal" *JAMA* 1970 LXXIV 1229
- Marfan A B "Un cas de deformation congenitale des quatre membres plus prononcee aux extremités caracterisee par l'allongement des os avec un certain degre d'amincissement" *Bull et mem soc med hop d Paris* 1896 XIII 220
- Peacock T B "On Malformations of the Human Heart etc with Original Cases and Illustrations" John Churchill and Sons London 2nd ed 1866 (1st ed 1858)
- Rosler H "Beitrage zur Lehre von den angeborenen Herzfehlern I. Über die Röntgenbefunde bei angeborenen Herz Gefässmissbildungen (Herzfehlern)" *Wien Arch f inn Med* 1928 XV 487
- Spitzer A "Über den Bauplan des normalen und missbildeten Herzens (Versuch einer phylogenetischen Theorie)" *Arch Arch f path Anat* 1923 CCXLIII 81
- Swan C Tostevin A L Moore B Mayo H and Barham Black G H "Congenital Defects in Infants Following Infectious Diseases During Pregnancy With Special Reference to the Relationship between German Measles and Cataract Deaf Mutism Heart Disease and Microcephaly and to the Period of Pregnancy in Which the Occurrence of Rubella is Followed by Congenital Abnormalities" *M J Australia* 1943 II 201
- White P D and Jones T D "Heart Disease and Disorders in New England" *Am Heart J* 1928 III 302

#### Recent References (1944-1950)

- Alexander F and White P D "Four Important Congenital Cardiac Conditions Causing Cyanosis to be Differentiated from the Tetralogy of Fallot Tricuspid Atresia Eisenmenger's Complex Transposition of the Great Vessels and a Single Ventricle" *Ann Int Med* 1947 XXVII 64
- Barclay A E Franklin K J and Prichard M M L "The Foetal Circulation and Cardiovascular System and the Changes That They Undergo at Birth" Blackwell Scientific Publications Ltd Oxford 1944
- Campbell M "Genetic and Environmental Factors in Congenital Heart Disease" *Quart J Med* 1949 XVIII 379
- Clawson B J "Types of Congenital Heart Disease in 15 597 Autopsies" *J Lancet* 1944 LXIV 114
- Dexter L "Cardiac Catheterization in Diagnosis of Congenital Heart Disease" *Bull New York Acad Med* 1950 XXVI 91
- Dexter L Haynes F W Burwell C S Eppinger E C Seibel R E and Evans J M "Studies of Congenital Heart Disease I. Technique of Venous Catheterization as a Diagnostic Procedure" *J Clin Investigation* 1947 XXVI 547
- III "Venous Catheterization as a Diagnostic Aid in Patent Ductus Arteriosus, Tetralogy of Fallot Ventricular Septal Defect and Auricular Septal Defect" *Ibid* 1947 XXVI 561
- Donzelot E Emam Zade A M Heim de Balsac R and others "Langiocardiographie dans les cardiopathies congenitales: interpretation valeur indications" *Semaine d Hop de Paris* 1949 XXV 2309
- Dry T J et al "Congenital Anomalies of the Heart and Great Vessels" Charles C Thomas Publisher Springfield Illinois 1948
- Gates E M Rogers H M and Edwards J E "Syndrome of Cerebral Abscess and Congenital Cardiac Disease" *Proc Staff Meet Mayo Clin* 1947 XXII 401

- Gregg N M "Rubella During Pregnancy of the Mother with Its Sequelæ of Congenital Defects in the Child" *M J Australia* 1945 I 313
- McQuiston W O "Anesthesia in Cardiac Surgery Observations on Three Hundred and Sixty-two Cases" *Arch Surg* 1950 LXI 892
- Mannheimer E *Morbus Caeruleus An Analysis of 114 Cases of Congenital Heart Disease with Cyanosis* S Karger Basle Suisse and New York 1949
- Maronde R F Brain Abscess and Congenital Heart Disease *Ann Int Med* 1950 XXXIII 602
- Mlezech F and Salzmann F "Thorakoskopie bei angeborenen Herzfehlern" *Wien Ztschr für inn Med* 1950 XXXI 442
- Murray G "Closure of Defects in Cardiac Septa" *Ann Surg* 1948 CXXVIII 843
- Paul O Myers G S and Campbell J A "The Electrocardiogram in Congenital Heart Disease A Preliminary Report" *Circulation* 1951 III 564
- Perez de los Reyes W de la Torre H and Douglas R Remarks About 500 Cases of Cardiovascular Congenital Malformations Examined in the Cardiological Department of the Infants Municipal Hospital in Habana During the Last Thirteen Years" *Am Heart J* 1949 XXXVII 661
- Tausig H B *Congenital Malformations of the Heart* The Commonwealth Fund New York, 1947
- Analysis of Malformations of the Heart Amenable to a Blalock Taussig Operation" *Am Heart J* 1948 XXXVI 321
- Thordarson O "Clinical Studies on Relative Incidence of Congenital Heart Disease" *A 33 med Scandinav* 1947 CXXVII 233
- Tobin J R Jr Bay E B and Humphreys E E "Marfan's Syndrome in Adult Dissecting Aneurysm of Aorta Associated with Arachnodactyly" *Arch Int Med* 1947 LXXX 475
- Tubbs O S "The Surgery of Congenital Heart Disease" *Brit Heart J* 1948 X, 77
- Wesselhoefst C. Rubella (German Measles) and Congenital Deformities *New Eng Land J Med* 1949 CCXL 258

### Dextrocardia

- Churchill E D and Adams F D "Situs Inversus Sinusitis Bronchiectasis Report of 5 Cases Including Frequency Statistics" *J Thoracic Surg* 1937 VII 206
- Rosler H Beiträge zur Lehre von der angeborenen Herzfehlern VI Über die angeborene isolierte Rechtslage des Herzens" *Wien Arch f inn Med* 1930 XIX 505

### Congenital Hypertrophy (Including the So-called Idiopathic)

(See also under Coronary Anomalies)

- Howland J Idiopathic Hypertrophy of the Heart in Young Children *Contributions to Medical and Biological Research* dedicated to Sir William Osler 1919 I 582
- Hubbard J E Paroxysmal Tachycardia and Its Treatment in Young Infants" *Am J Dis Child* 1941 LXI 687
- Kugel M A and Stoloff E G "Dilatation and Hypertrophy of the Heart in Infants and in Young Children With Myocardial Degeneration and Fibrosis (So-called Congenital Idiopathic Hypertrophy)" *Am J Dis Child* 1933 XLV 828
- Pompe J C Hypertrophie idiopathique du coeur" *Ann d'anat path et d'anat norm med chir* 1933 X 23
- von Gierke F Hepato-nephromegalia glycogenica *Beur path Anat u z allg Path* 1929 LXXXII 497

### Interatrial Septal Defects

- Abbott M E Two Cases of Widely Patent Foramen Ovale" *Bull Internat A M Museums* 1915 V 129
- Asley J M and Kahler J E "Longevity in Extensive Organic Heart Lesions A Case of Lutembacher's Syndrome in a Man Aged 72" *Ann Int Med* 1950 XXXIII 1031
- Barber J M Magidson O and Wood P Atrial Septal Defect With Special Reference to the Electrocardiogram the Pulmonary Artery Pressure and the Second Heart Sound" *Brit Heart J* 1950 XII 277

- Bedford D E Papp C and Parkinson J "Atrial Septal Defect" *Brit Heart J* 1941 III 37
- Bonnabel J *Contribution à l'étude de quelques affections congénitales du cœur compatibles avec l'existence et de leur pronostic* Thesis Paris 1906-7
- Christie A "Normal Closing Time of the Foramen Ovale and the Ductus Arteriosus An Anatomic and Statistical Study" *Am J Dis Child* 1930 XL 323
- Cournand A Motley H L Himmelstein A Dresdale D and Baldwin J "Recording of Blood Pressure from the Left Auricle and the Pulmonary Veins in Human Subjects with Interatrial Septal Defect" *Am J Physiol* 1947 CL 267
- Dow J W and Dexter L "Circulatory Dynamics in Atrial Septal Defect" *J Clin Investigation* 1950 XXIX 809
- Ellis F R Greaves M and Hecht H H "Congenital Heart Disease in Old Age Interatrial Septal Defect with Mitral and Tricuspid Valvulitis" *Am Heart J* 1950 XL 154
- Firket C "Examen anatomique d'un cas de persistance du trou ovale de Botal avec lésions valvulaires considérables du cœur gauche chez une femme de 74 ans" *Ann soc med-chir Liege* 1880 XIX 188
- Ingham D W "Paradoxical Embolism" *Am J M Sc* 1938 CXCVI 201
- Lutmbacher D "De la stenose mitrale avec communication interauriculaire" *Arch d mal d coeur* 1916 IX 237
- McGinn S and White P D "Interatrial Septal Defect Associated with Mitral Stenosis" *Am Heart J* 1933 IX 1
- Patten B M "Closure of Foramen Ovale" *Am J Anat* 1911 XLVIII 19
- Roesler H "Interatrial Septal Defect" *Arch Int Med* 1923 LIV 339
- Seib G A "Incidence of Patent Foramen Ovale Cordis in Adult American Whites and American Negroes" *Am J Anat* 1934 LV 511
- Selzer A and Lewis A E "The Occurrence of Chronic Cyanosis in Cases of Atrial Septal Defect" *Am J M Sc* 1949 CCXVIII 516
- Swan H Maresh G Johnson M E and Warner G "The Experimental Creation and Closure of Auricular Septal Defects" *J Thoracic Surg* 1950 XX 542
- Uhley M H "Lutembacher's Syndrome and a New Concept of the Dynamics of Interatrial Septal Defects" *Am Heart J* 1942 XXIV 315

### Interventricular Septal Defects

- Donzelot E Emam Zade A M Heim de Balsac R. and Kolosy M "Le complexe d'Eisenmenger Étude de 29 cas" *Arch d mal d coeur* 1949 XLII 118
- Eisenmenger V "Die angeborenen Defecte der Kammerscheidewand des Herzens" *Ztschr f klin Med* 1897 XXXII Supplement H ft. 1
- Roger H "Recherches cliniques sur la communication congénitale des deux cœurs par l'occlusion du septum interventriculaire" *Bull d l'Acad d med d Paris* 1879 VIII 1074
- Rokitansky C "Die Defecte der Scheidewande des Herzens" Braumuller Vienna 1875
- Rosedale R S "Interventricular Septal Defect Dextroposition of Aorta and Dilatation of Pulmonary Artery Report of Case with Structural Pathogenesis" *Am J Path* 1935 XI 333
- Selzer A "Defect of the Ventricular Septum Summary of Twelve Cases and Review of the Literature" *Arch Int Med* 1949 LXXXIV 798
- Selzer A and Laqueur G L "The Eisenmenger Complex and Its Relation to the Uncomplicated Defect of the Ventricular Septum Review of Thirty five Autopsied Cases of Eisenmenger's Complex Including Two New Cases" *Arch Int Med* 1951 LXXXVII 218

### Pulmonary Stenosis

- Blalock A and Kieffer R F Jr "Valvulotomy for Relief of Congenital Valvular Pulmonic Stenosis with Intact Ventricular Septum Report of 19 Operations by the Brock Method" *Ann Surg* 1950 CXXXII 496
- Brock W C "Pulmonary Valvulotomy for Relief of Congenital Pulmonary Stenosis" and "Surgery of Pulmonary Stenosis" *Brit M J* 1948 I 1121 and 1949 II 399

- Brock H C and Campbell M Valvulotomy for Pulmonary Valvular Stenosis *Brit Heart J* 1950 XII 377
- Infundibular Resection or Dilatation for Infundibular Stenosis *Ibid* 1950 XII 403
- Currens J H Kinney T D and White P D Pulmonary Stenosis with Intact Interventricular Septum Report of Eleven Cases *Am Heart J* 1945 XXX 491
- Engle M A and Taussig H B Valvular Pulmonic Stenosis with Intact Ventricular Septum and Patent Foramen Ovale Report of Illustrative Cases and Analysis of Clinical Syndrome *Circulation* 1950 II 481
- Genovese P D and Rosenbaum D Pulmonary Stenosis with Survival to the Age of 78 Years *Am Heart J* 1951 XLI 755
- Joly Fr Carloti J Sicut J R and Piton A Cardiopathies congenitales II Les trilogies de Fallot *Arch d mal d coeur* 1950 XLIII 687
- Potts W J Surgical Treatment of Congenital Pulmonary Stenosis *Ann Surg* 1949 CXXX, 342
- Potts W J and Gibson E Aortic Pulmonary Anastomosis in Congenital Pulmonary Stenosis Report of Forty five Cases *JAMA* 1948 CXXXVII 343
- Potts W J Gibson S Riker W L and Leininger C R Congenital Pulmonary Stenosis with Intact Ventricular Septum *JAMA* 1950 CXLIV 8
- Potts W J Smith S and Gibson E Anastomosis of Aorta to Pulmonary Artery *JAMA* 1946 CXXXII 627
- Selzer A Carnes W H Noble C A Jr and others "Syndrome of Pulmonary Stenosis with Patent Foramen Ovale *Am J Med* 1949 VI 3
- White P D Hurst J W and Fennell R H Survival to the Age of Seventy five Years with Congenital Pulmonary Stenosis and Patent Foramen Ovale *Circulation* 1950 II 358
- Tetralogy of Fallot**
- Bialock A and Taussig H B Surgical Treatment of Malformations of Heart *JAMA* 1945 CXXVIII 189
- Donzelot, E Heim de Balsac R Emam Zade A M Escalle J E and Metianu C Étude de 200 cas de tetrade de Fallot *Arch d mal d coeur* 1949 XLII 98
- Fallot A Contribution à l'Anatomie pathologique de la Maladie bleue (Cyanose cardiaque) *Marseilles méd* 1888 XXV 77 138 207 270 and 403
- Hunter W Three Cases of Malconformation in the Heart *Med obs soc phys London* 1784 VI 291
- Sandifort E *Observations anatomico pathologicae* Ludg Bat P v d Eyk et D Vygh 1777 Chap 1 Fig 1
- Stensen Niels (Nicholaus Steno) In Bartholin Thomas *Acta medica et philosophica Hafniensia* 1671-1672 I 202 Reprinted in Stenon Nicolai *Opera philosophica* 2 49-53 edited by Vilhelm Maar Copenhagen 1910
- Talbott J H et al A Record Case of the Tetralogy of Fallot with Comments on Metabolic and Pathologic Studies *Am Heart J* 1941 XXII 754
- White P D and Sprague H B The Tetralogy of Fallot Report of a Case in a Noted Musician Who Lived to His Sixtieth Year *JAMA* 1929 XCII 787
- Other Valvular and Ostial Defects**
- Abbott M E On the Relative Incidence and Clinical Significance of a Congenitally Bicuspid Aortic Valve *Libman Anniversary Volumes* 1932 I 1
- Campbell J M Artificial Aortic Valve Preliminary Report *J Thoracic Surg* 1950 XIX 312
- Donnelly H H Congenital Mitral Stenosis Report of a Case of Developmental Mitral Stenosis Combined with Hypoplasia of Left Ventricle and Left Auricle Rudimentary Aorta and Other Developmental Defects *JAMA* 1924 LXXXII 1318
- Ebstein W Ueber einen sehr seltenen Fall von Insuffizienz der Valvula tricuspidalis bedingt durch eine angeborene hochgradige Missbildung derselben *Arch f Anat u Physiol* 1866 p 238
- Engle M A Payne T P B Bruns C and Taussig H B Ebstein's Anomaly of the Tricuspid Valve Report of Three Cases and Analysis of Clinical Syndrome *Circulation* 1950 I 1246

- Fell E H Gasul B M Davis C B Jr and Casas R Surgical Treatment of Tricuspid Atresia *Arch Surg* 1949 LIX 445
- Gasul B M Fell E H Marino J J and Davis C B Jr Tricuspid Atresia Report of Two Cases of Young Infants with Successful Operation" *Am J Dis Child* 1949 LXXVIII 16
- Lewis T and Grant R T Observations Relating to Subacute Infective Endocarditis Part I Notes on the Normal Structure of the Aortic Valve Part II Bicuspid Aortic Valves of Congenital Origin *Heart* 1923 X 21
- Sommers S C and Johnson J M Congenital Tricuspid Atresia *Am Heart J* 1951 XLI 130
- Sternberg C "Ueber infravalvuläre Konusstenosen Zur Pathologie der Grenze zwischen Herzmuskulatur und Herzskelett (A discussion of subaortic and subpulmonary infundibular stenosis) *Verhandl d deutsch path Gesellsch* 1930 XXV 238
- Taussig H B Clinical and Pathological Findings in Congenital Malformations of Heart Due to Defective Development of Right Ventricle Associated with Tricuspid Atresia or Hypoplasia *Bull Johns Hopkins Hosp* 1936 LIX 435
- Yater W M and Shapiro M J "Congenital Displacement of the Tricuspid Valve (Ebstein's Disease) Review and Report of a Case with Electrocardiographic Abnormalities and Detailed Histologic Study of the Conduction System *Ann Int Med* 1937 XI 1043

### Heart Block

- Campbell M Congenital Complete Heart Block *Brut Heart J* 1943 V 15
- Carter E P and Howland J A Note Upon the Occurrence of Congenital Atrioventricular Dissociation Report of a Case of Congenital Complete Heart Block *Bull Johns Hopkins Hosp* 1920 XXXI 351
- Plant R K and Steven R A Complete A V Block in a Fetus *Am Heart J* 1945 XXX 615
- Wilson J G and Grant R T A Case of Congenital Malformation of the Heart in an Infant Associated with Partial Heart Block *Heart* 1926 VII 295 (The first autopsy report)
- Yater W M Congenital Heart Block Report of a Case with Incomplete Heterotaxy *Proc Staff Meet Mayo Clin* 1928 III 320

### Coarctation of the Aorta

- Abbott M E "Coarctation of the Aorta of the Adult Type II Statistical and Historical Retrospect of 200 Recorded Cases with Autopsy of Stenosis or Obliteration of the Descending Arch *Am Heart J* 1928 III 574
- Blackford L M Coarctation of the Aorta *Arch Int Med* 1928 XLI 70
- Christensen N A and Hines E A Jr Clinical Features in Coarctation of the Aorta A Review of 96 Cases *Proc Staff Meet Mayo Clin* 1948 XXIII 339
- Crafoord C and Nylm G "Congenital Coarctation of Aorta and Its Surgical Treatment" *J Thoracic Surg* 1945 XIV 347
- Freeman N E Miller E R Stephens H B and Olney M B Retrograde Arteriography in the Diagnosis of Cardiovascular Lesions II: Coarctation of the Aorta *Ann Int Med* 1950 XXXII 827
- Graybiel A Allen A W and White P D "Histologic Study of Arterioles of Muscle and Skin from Arm and Leg in Individuals with Coarctation of the Aorta" *J Clin Investigation* 1935 XIV 52
- Gross R E Surgical Correction for Coarctation of Aorta *Surgery* 1945 XVIII 673
- "Coarctation of the Aorta Treatment of One Hundred Cases" *Circulation* 1950 I 41
- Johnson J and Kirby C K "Surgical Treatment of Infantile Type of Coarctation of Aorta" *Ann Surg* 1948 CXXVII 1119
- Lewis T "Material Relating to Coarctation of the Aorta of the Adult Type" *Heart* 1933 XVI 205
- Morgagni J B *De Sedibus et Causis Morborum Typographia Remondiniana Venice* 1761

- Nickerson J L, Humphreys G H, Deterling R A, Fleming T C and Mathers J A L. "Diagnosis of Coarctation of the Aorta with the Aid of the Low Frequency Critically Damped Ballistocardiograph" *Circulation* 1950 1 1032
- Pereiras R and Castellanos A. "Retrograde Aortography Its Value in Diagnosis of Coarctation of Aorta by Means of New Indirect Sign" *Radiology* 1949 LIII 859
- Potts W J. "Technic of Resection of Coarctation of Aorta with Aid of New Instruments" *Ann Surg* 1950 CXXXI 466
- Reifenstein G H, Levine S A and Gross R E. "Coarctation of the Aorta" *Am Heart J* 1947 XXXIII 146
- Steele J M and Cohn A E. "The Nature of Hypertension in Coarctation of the Aorta" *J Clin Investigation* 1938 XVII 514
- Taylor B E et al. "Patent Ductus Arteriosus Associated with Coarctation of the Aorta Report of 2 Cases Studied Before and After Surgical Treatment" *Proc Staff Meet Mayo Clin* 1950 XXV 62
- Walker W B. "Coarctation of the Aorta in Father and Son" *New England J Med* 1934 CCXI 1192

#### Other Anomalies of the Aorta

- Arkin A. "Double Aortic Arch with Total Persistence of the Right and Isthmus Stenosis of the Left Arch. A New Clinical and X ray Picture. Report of Six Cases in Adults" *Am Heart J* 1936 XI 444
- Baer R W, Taussig H H and Oppenheimer E H. "Congenital Aneurysmal Dilatation of Aorta Associated with Arachnodactyly" *Bull Johns Hopkins Hosp* 1943 LXXII 309
- Bain C W C and Parkinson J. "Common Aorto Pulmonary Trunk. A Rare Congenital Defect" *Brit Heart J* 1943 V 97
- Downing D F. "Congenital Aortic Septal Defect" *Am Heart J* 1950 XL 285
- Gross R H and Ware P F. "Surgical Significance of Aortic Arch Anomalies" *Surg Gynec & Obst* 1946 LXXXIII 435
- Herbut P A. "Anomalies of Aortic Arch" *Arch Path* 1943 XXXV 717
- Ingalls N W. "Truncus Arteriosus Communis Persistens" *Anat Rec* 1915 X 9
- King, P H et al. "Aortic Septal Defect Simulating Patent Ductus Arteriosus" *J Mt Sinai Hosp* 1951 XVII 310
- MacGilpin H H Jr. "Truncus Arteriosus Communis Persistens" *Am Heart J* 1950 XXXIX, 615
- Monie I W and DePape A D J. "Congenital Aortic Atresia. Report of One Case with an Analysis of 26 Similar Reported Cases" *Am Heart J* 1950 XL 595
- Morrison R W and Edwards J E. "Subaortic Stenosis. Report of Two Cases One Associated with Patent Ductus Arteriosus the Other Complicated by Bacterial Endocarditis" *Bull Internat A M Museums* 1950 XXXI 73
- Perelman H and Putschar W G J. "Congenital Communication Between Aorta and Pulmonary Artery. Report of a Case and Review of the Literature" *Bull Internat A M Museums* 1949 XXX, 1
- Rokitansky C. *Die Defecte der Scheidewinde des Herzens*. Braumüller, Vienna 1875
- Spencer H and Dworken H J. "Congenital Aortic Septal Defect with Communication Between Aorta and Pulmonary Artery. Case Report and Review of Literature" *Circulation* 1950 II 880
- Sprague H H, Ernlund C H and Albright F. "Clinical Aspects of Persistent Right Aortic Root" *New England J Med* 1933 CCIX, 679
- Wolman, I J. "Syndrome of Constricting Double Aortic Arch in Infancy" *J Pediatr* 1939 XIV 527

#### Transposition of the Great Arterial Trunks

- Blalock A and Hanlon C R. "Surgical Treatment of Complete Transposition of Aorta and Pulmonary Artery" *Surg Gynec & Obst* 1950 XC 1
- Harris J S and Farber S. "Transposition of Great Cardiac Vessels with Special Reference to Phylogenetic Theory of Spitzer" *Arch Path* 1939 XXVIII 427
- Spitzer A. "Über den Bauplan des normalen und missbildeten Herzens" *Furch Arch f path Anat* 1923 CCXLIII 81

- Taussig H H Complete Transposition of the Great Vessels *Am Heart J* 1938 XVI 728
- Taussig H B and Bing R J Complete Transposition of the Aorta and a Levoposition of the Pulmonary Artery Clinical Physiological and Pathological Findings *Am Heart J* 1949 XXVII 551

### Patent Ductus Arteriosus

- Adams F H LaBree J and Stauffer H M Right Heart Catheterization of Aorta Through a Patent Ductus Arteriosus Report of 2 Cases *Pediatrics* 1950 V 390
- Botallo Quoted by Puschmann *Handbuch geschichte der med* in 1903 II 235 footnote 9 (Botallo in his anatomical observations named *L Opera omnia Vena arteriarum nutrita a nullo Danielis and Abrahami Gaasbeeck* 1660 p 66)
- Bourne G et al Ligation and Chemotherapy for Infection of Patent Ductus Arteriosus *Lancet* 1941 II 444
- Burwell C S Eppinger E C and Gross R E "The Effects of Patency of the Ductus Arteriosus on the Circulation" *J Clin Investigation* 1940 XIX 774 and 1941 XX 127
- Donovan M S Neuhauser E D and Sosman M C Roentgen Signs of Patent Ductus Arteriosus Summary of 50 Surgically Verified Cases" *Am J Roentigenol* 1943 L 293
- Fishman L and Silverthorne M C "Persistent Patent Ductus Arteriosus in the Aged Including the Report of the Oldest Case on Record with Diagnosis Confirmed Post Mortem" *Am Heart J* 1951 XLI 762
- Graybiel A Strieder J W and Boyer N H An Attempt to Obliterate the Patent Ductus Arteriosus in a Patient with Subacute Bacterial Endocarditis *Am Heart J* 1938 XV 621
- Gross R E Complete Division for Patent Ductus Arteriosus *J Thoracic Surg* 1947 XVI 314
- Gross R E and Hubbard J B "Surgical Ligation of a Patent Ductus Arteriosus Report of First Successful Case" *JAMA* 1939 CXII 729
- Josefson A Offenstehender Ductus Botalli nebst Atherom in den Asten der Arteris pulmonalis" *Nord med ark* Stockholm 1897 ns VII No 10 p 1
- Kjaergaard H "Patent Ductus Botalli in Three Sisters" *Acta med Scandinav* 1946 CCXV 330
- Myers G S et al Atypical Patent Ductus Arteriosus with Absence of the Usual Aortic Pulmonary Pressure Gradient and of the Characteristic Murmur" *Am Heart J* 1951 XLI 819
- Pritchard W H Brofman B L and Hellerstein H K Clinical Studies in Reversal of Flow in Patent Ductus Arteriosus" *J Lab & Clin Med* 1950 XXXVI 974
- Ravin A and Darley W Apical Diastolic Murmurs in Patent Ductus Arteriosus *Ann Int Med* 1950 XXXIII 903
- Shapiro M J and Keys A "Prognosis of Untreated Patent Ductus Arteriosus and Results of Surgical Intervention Clinical Series of 50 Cases and Analysis of 139 Operations" *Am J M Sc* 1943 CCVI 174
- Touff A W S and Vesell H "Experiences in Surgical Treatment of Subacute Streptococcus Viridans Endarteritis Complicating Patent Ductus Arteriosus" *J Thoracic Surg* 1940 X 59
- Walker G C and Ellis L B "The Familial Occurrence of Congenital Cardiac Anomalies" *Proc New England Heart A* 1940-41 p 26
- White P D "Patent Ductus Arteriosus in a Woman in Her Sixty sixth Year" *JAMA* 1928 XCI 1107

### Defects of the Great Veins

- Abbott O A "Congenital Aneurysm of Superior Vena Cava Report of One Case with Operative Correction" *Ann Surg* 1950 CXXXI 259
- Curtis A C and Helms R W Congenital Absence of the Valves in the Veins as a Cause of Varicosities" *Arch Dermat & Syph* 1947 LV 639
- Dotter C T Hardisty N M and Steinberg I "Anomalous Right Pulmonary Vein Entering the Inferior Vena Cava Two Cases Diagnosed During Life by Angiocardiography and Cardiac Catheterization" *Am J M Sc* 1949 CCXVIII 31

- Gi espie J E O'N Pulmonary Venous Return via Superior Vena Cava *Brit Heart J* 1941 III 241
- MacCready P II Anomalies of the Pulmonary Veins *Bull Johns Hopkins Hosp* 1918 XXIX 271
- Papez J W "Two Cases of Persistent Left Superior Vena Cava in Man *Anat Rec* 1938 LXX 191
- Smith J C Anomalous Pulmonary Veins *Am Heart J* 1951 XLI 561
- Younis M O Common Trunk of Pulmonary Veins Tributary to Portal Vein, with Multiple Cardiac Anomaly *Arch Path* 1947 XLIV 169

### Coronary Anomalies

- Bland E F White P D and Garland J Congenital Anomalies of the Coronary Arteries Report of an Unusual Case Associated with Cardiac Hypertrophy *Am Heart J* 1933 VIII 787
- Eidlow S and Mackenzie E R Anomalous Origin of the Left Coronary Artery from the Pulmonary Artery Report of a Case Diagnosed Clinically and Confirmed by Necropsy *Am Heart J* 1946 XXXII 243
- Gasul B M and Loeffler E "Anomalous Origin of the Left Coronary Artery from the Pulmonary Artery (Bland White Garland Syndrome) Report of Four Cases *Pediatrics* 1949 III 498
- Jordan R A Dry T J and Edwards J E "Cardiac Clinics CXXXVI Anomalous Origin of the Right Coronary Artery from the Pulmonary Trunk *Proc Staff Meet Mayo Clinic* 1950 XXV 673
- Krumbhaar E B and Ehrlich W E Varieties of Single Coronary Artery in Man Occurring as Isolated Cardiac Anomalies *Am J M Sc* 1938 CXCVI 407
- Smith J C Review of Single Coronary Artery with Report of 2 Cases *Circulation* 1950 I 1168
- White N K and Edwards J E "Anomalies of the Coronary Arteries Report of Four Cases" *Arch Path* 1948 XLV 766

### Miscellaneous

- Chiari H Ueber Netzbildungen im rechten Vorhofe des Herzens *Beitr z path Anat u allg Path* 1897 XXII 1
- Collins D C Anomalous Papillary Muscle Attached to Pulmonary Valve of Heart *Am Heart J* 1931 VII 79
- Gross R E Bill A H Jr and Peirce E C Methods for Preservation and Transplantation of Arterial Grafts Observations on Arterial Grafts in Dogs Report of Transplantation of Preserved Arterial Grafts in Nine Human Cases *Surg Gynec & Obst* 1949 LXXXVIII 689
- Gross R E and Neuhauser E II Compression of Trachea or Esophagus by Vascular Anomalies Surgical Therapy in 40 Cases *Pediatrics* 1951 VII 69
- Hamilton W F and Byers R Aortic Disease with Anomalous Signs Due to Aberrant Chordae Tendineae *Montreal M J* 1899 XXVIII 508
- Hirschboeck F J Aneurysm of One of the Sinuses of Valsalva Caused by a Congenital Lesion Case Report *Am Heart J* 1942 XXIV 550
- Huchard H Contribution a l'etude clinique des tendons aberrants du coeur *Rev de med* 1893 XIII, 113
- Lindeboom G A and Bouwer W F Dissecting Aneurysm (and Renal Cortical Necrosis) Associated with Arachnodactyly (Marfan's Disease) *Cardiologia* 1949 XV 12
- Parsons C G Cor Triatriatum Concerning the Nature of an Anomalous Septum in the Left Auricle *Brit Heart J* 1950 XII 327
- Rogers H M and Edwards J E "Cor Triloculare Biatrum An Analysis of the Clinical and Pathologic Features of Nine Cases *Am Heart J* 1951 XLI 299
- Sinclair J G "A Five-Chambered Human Heart" *Anat Record* 1944 XC, 41
- Soulie P Servelle M Barreau A Schweisguth O and Rougeulle J "Greffes arterielles dans le traitement des malformations congenitales du coeur" *Presse med* 1950 LVIII 761
- Yater W M "Variations and Anomalies of the Venous Valves of the Right Atrium of the Human Heart *Arch Path* 1929 VII 418



## RHEUMATIC HEART DISEASE

---

**Introduction** Although at present apparently and happily on the decline one of the three most common and serious types of heart disease is rheumatic, the other two are hypertensive and coronary. The relative incidence of these types varies greatly in different parts of the world in fact in different parts of the United States of America for example in New England more than twenty years ago the proportions were recorded as approximately 40, 29 and 36 per cent respectively with some overlapping of the latter two (White and Jones 1928) in Virginia 22, 46 and 46 per cent respectively (Wood Jones and Kimbrough 1926) in San Francisco somewhat more recently 22, 22 and 40 per cent respectively (Geiger et al 1936), and in Texas 10, 45 and 24 per cent for the whites and 4, 51 and 6 per cent for the Negroes (Stone and Vanzant 1927). A reappraisal of these percentages is now in order because of the possibility of a changing incidence as well as of more accurate statistics. Recent papers for example report 13.8 per cent among 436 cases of organic heart disease for Southwestern Virginia (Glendy 1948) 11.7 cases of rheumatic heart disease (11 per cent) as found among 1 045 cardiac autopsies in another southern group (Holoubeck and Holoubeck 1947) and 26.9 per cent of 519 cardiacs in the Rocky Mountains (Cannon 1946). A recent review of 3 000 cases of heart disease in New England (White 1951) has given percentages of 23.5, 26.2 and 48.5 respectively for rheumatic hypertensive and coronary heart disease. Thus climatic conditions and to a much less extent race have seemed to be important controlling factors as will be noted in more detail later. Other relationships that have become more and more evident in the past few decades are familial susceptibility social and economic status with particular reference to crowding and the hemolytic streptococcus as an exciting factor these will be discussed shortly.

One of the most important reasons why rheumatic heart disease is so serious is the fact that it is particularly a disease of youth crippling and killing many children and young adults. As a result many medical investigators and special

practitioners and social workers have undertaken campaigns to study the various problems involved and to reduce this menace and scourge which has assumed somewhat the role once held by the white plague tuberculosis. During the fifteen year age period from 5 to 20 rheumatic fever with heart disease is in the United States the leading cause of death, and at ages 20 to 25 it is second only to tuberculosis (Armstrong and Wheatley *Studies in Rheumatic Fever* Metropolitan Life Insurance Company Nov. 1944). In New York City in 1938 there were 1105 deaths reported from rheumatic fever and rheumatic heart disease as compared with a combined total of 247 from whooping cough, meningitis, measles, diphtheria, scarlet fever and poliomyelitis (see Figure 81).

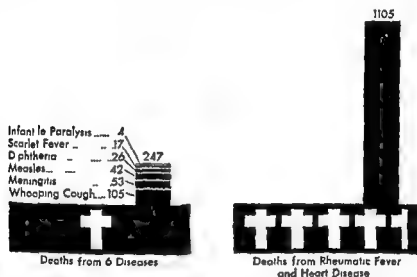


FIG 81 Deaths from rheumatic fever and heart disease compared with deaths from six other common infectious diseases New York City 1938. Data compiled by Dr Homer Swift (kindness of Dr David I. Rutstein and the American Public Health Association New York.)

Already however either as the result of special efforts or because of an amelioration of the rheumatic infection itself or both or most likely of all because of considerable improvement in living conditions there is some indication that in the last three decades (1920 to 1950) there has been a slight but definite decline both in the severity and in the incidence of rheumatic heart disease (Hedley 1939 Wheatley 1949) evidences of which have been a drop from 27 cases per thousand patients in the wards of the Massachusetts General Hospital during the years from 1927 to 1930 to 22 cases per thousand during the years from 1937 to 1940 and finally 15 cases per thousand during the years from 1947 to 1950 a decrease from 26 cases per thousand at the Boston Floating Hospital in the years 1933 to 1937 to 9 per thousand from 1943 to 1947 and to 6 per thousand in 1948 and 1949 (kindness of Dr

James Baty) the complete clearing of a formerly long waiting list of children with rheumatic fever for admission to the House of the Good Samaritan in Boston, the decrease in rheumatic heart disease found recently in the school children of Denver Colorado and a drop of relative incidence of rheumatic heart disease among cardiac admissions to the John Sealy Hospital in Galveston from 7.6 per cent in the decade 1920-1929 to 2.1 per cent in the decade 1930-1939 (Dechard and Herrmann, 1943)

The broad term 'rheumatic heart disease' includes acute, subacute and chronic involvement of the heart of the 'rheumatic' type (as discussed under the heading Pathology to follow) whether or not a clear cut history of rheumatic fever can be elicited. The rheumatic infection itself is manifested by a widespread reaction of the tissues throughout the body in this respect resembling tuberculosis and syphilis on the one hand and allergy on the other. In fact the terms 'rheumatic granulomatosis', 'the rheumatic state' and 'rheumaticosis' have been suggested as better than the usual expressions 'rheumatic polyarthritis', 'rheumatic fever', and 'the rheumatic infection' (Fahr 1929, Coburn 1931, Graham 1932).

**Etiology Cause.** The cause of the rheumatic infection that plays such havoc in the heart is not yet clear. It is the subject of intensive research at the present time and the solution of the problem is awaited with the keenest interest. Streptococci of various types have been considered in some way responsible for many years and especially the hemolytic streptococcus (Coburn and others). The general consensus of opinion is that the *Streptococcus hemolyticus* is the chief exciting factor which precipitates the so-called rheumatic state throughout the body particularly in the heart. Other exciting factors have however been noted such as typhoid vaccine (Bland and Jones 1935) and even injuries suggesting that the exciting factor is not specific nevertheless an acute streptococcus infection appears responsible in the vast majority of the cases. The finding of streptococci or other bacteria in the blood, joint fluid or pericardial or pleural fluid of acute rheumatic cases has been occasionally reported but is not considered of primary importance any more than the finding of immunologic reactions in tissues or blood. A decade or two ago a virus origin of the disease was suggested but this has never been confirmed. Whether the tissue reactions throughout the body are due directly to bacterial toxin or result indirectly from an intermediary agent or as an allergic response has not yet been settled. Something akin to the last mentioned hypothesis with particular involvement of the body's collagen is at present thought to be most likely but much research on this problem is in progress.

In recent years there have arisen interesting speculations concerning the possible role in the production of rheumatic fever of the action of hyaluronidase, an enzyme on hyaluronic acid, a mucopolysaccharide which with chondroitin sulfate is an important element in the ground substance of connective tissue, synovial fluid and certain other parts of the body. Certain strains of hemolytic streptococci produce hyaluronic acid and hyaluronidase and

salicylates have been reported to exert an antihyaluronidase effect. The possible etiologic relationships suggested by these findings and by the effects of hormones (ACTH and cortisone) need much further study before definite conclusions can be established.

*Place of entry* The place of entry of the rheumatic organism or virus (if such exists) into the body is probably the mouth. The faucial tonsils have been considered to be the chief portal partly because their acute infection frequently ushers in acute rheumatic fever and partly because endocarditis may follow tonsillitis directly without any rheumatic symptoms. However other lymphoid tissue in the pharynx and nose may also harbor the rheumatic or activating organism and the gastrointestinal tract and foci of infection in sinuses and middle ear have not been ruled out as possible sources of rheumatic heart disease.

Rheumatic fever and chorea have been for many years regarded as the chief manifestations of the rheumatic infection that causes heart disease but tonsillitis, growing pains, and in very young children certain ill defined fevers or illnesses have been thought to be allied as lesser and somewhat uncertain evidences of the same infection. The separation between these definite entities of rheumatic fever and chorea and the indefinite infections or symptoms mentioned and between the latter and distinctly nonrheumatic diseases is ill defined in our present state of knowledge; the borderline must be regarded as very wide. Thus the diagnosis of a rheumatic infection or of rheumatic endocarditis or heart disease still often remains a matter of opinion. Two generations ago as now it was rather the custom to consider all infectious heart disease in young people that was not of syphilitic or of malignant bacterial nature to be rheumatic in origin. One generation ago there arose the belief that septic infection of nonrheumatic type was frequently responsible when a rheumatic history was not obtainable. Probably the truth rests somewhere between these views, namely that the large majority of cases of infectious endocarditis are rheumatic in origin but that some arise from other infections particularly terminal in nature even when not of malignant bacterial type.

The more carefully one investigates the past history of patients with the rheumatic type of chronic heart disease the more often one discovers a partly forgotten or mild rheumatism or chorea in such patients. On the other hand a prejudicial view is inclined to interpret every tonsillar infection or muscle ache as rheumatic. Furthermore rheumatic fever does not frankly appear as such in the first few years of life except in rare instances; children affected with chronic endocarditis following some poorly defined illness in the second or third year of life are likely later to develop definite chorea or rheumatic fever with recurrent infection of the heart. It is safest to regard and to treat as rheumatic all infectious heart disease of childhood (unless it is malignant bacterial endocarditis) even though occasionally the cause is not clearly the rheumatic infection; the term rheumatic type of heart disease acute sub-

acute or chronic covers satisfactorily, for the present at least the cases of doubtful etiology

A definite history of rheumatic fever, mild or severe can on careful investigation be found in 60 to 70 per cent of cases with 'rheumatic heart disease and in another 5 to 10 per cent a history of chorea without rheumatism is obtainable Chorea alone with no evidence of infection is not so often followed by heart damage (Jones and Bland 1935) earlier opinions to the contrary were based on failure to exclude infection particularly rheumatic fever

**Sex** Rheumatic heart disease attacks both sexes, but statistical analysis usually shows a more frequent incidence among females in the ratio of about 4 to 3 or 5 to 4 In one group of 956 cases there were 525 females and 431 males (White and Jones 1928) and in another group of 1 000 cases studied at the House of the Good Samaritan in Boston there were 709 females and 291 males, a 7 to 3 ratio but the preponderance of beds available for females accounts partly for this high ratio (Jones and Bland 1942)

**Age** In communities where rheumatic heart disease is common it is found in the great majority of cases between the ages of 4 years and 50 years It rarely begins in the first four years of life and is especially rare before the age of two years A case of intrauterine rheumatic heart disease has however been reported (Kissane and Koons 1933) also a case in an infant aged only 17 months has been noted (Schwarz 1932)

Most recently a group of 26 very young children with active rheumatic fever has been reported by Logue and Hurst (1951) of these 26 10 were under the age of four there being 3 three years old 5 two years old and 2 one year old there were also 9 who were four years old in this group 6 who were five years old and 1 whose exact age at the onset of rheumatic fever was not known but who was under five years of age Despite such exceptions long experience has shown that as a rule rheumatic heart disease begins between the ages of 4 and 15 years with height of onset between the seventh and eighth years It has been found that about 1 to 2 per cent of the school children in parts of the United States and Canada where rheumatic fever is prevalent have rheumatic heart disease varying greatly however from place to place or from one part of a city to another (from less than 0.5 per cent up to 4 or 5 per cent) largely dependent on the degree of crowding of living conditions (Robey 1927 Keith and Pequegnat 1947 Quinn 1948) Although some cases develop relatively late that is after the twentieth year of life this is distinctly unusual The mortality beginning in the first decade increases steadily and is highest in the second and fourth decades when infections (especially recurrent rheumatism) and heart failure take their toll Occasional instances of survival to the age of 70 years and a few even to 80 or over (White and Bland 1941) are seen when the cardiac damage has not been extensive The prevalence of rheumatic heart disease (*chronic as well as acute*) by decades in the New England group of 956 cases already noted (White and Jones 1928) as compared with that of 684 cases analyzed 25 years later (White 1951) was as follows

*Race* All civilized races and nationalities appear susceptible to rheumatic heart disease although a somewhat lower incidence has been noted in China than in parts of Europe and America of the same latitude. In New England people of English Scotch Irish Scandinavian French Polish Jewish German Italian and Negro stock have all been found with rheumatic heart disease.

Table 6

AGE GROUPING OF CASES OF RHEUMATIC HEART DISEASE  
IN NEW ENGLAND

Years	Group of 956 Cases Reported in 1928		Group of 684 Cases Reported in 1951	
	Cases	Percentage	Cases	Percentage
0-10	116	1.1	53	7.7
10-20	799	31.3	223	32.6
20-30	135	14.1	71	10.4
30-40	165	17.3	91	13.3
40-50	13	1.9	102	14.9
50-60	78	8.2	89	13.0
60-70	35	3.6	38	5.6
Over 70	5	.5	17	2.5
Total	956		684	

*Climate* Climate appears to be an important factor in the incidence both of the rheumatic infection and of the rheumatic type of heart disease. The colder wetter parts of the temperate zone particularly favor these conditions. It is also the colder and wetter seasons of the year—winter and spring in New England autumn and winter in old England. In the northern part of the United States the rheumatic infection and its permanent involvement of the heart are five times more frequent than in the southernmost part of the country or in the Philippine or Hawaiian Islands while in the midzone the incidence is between these two extremes. For example in Boston at the Peter Bent Brigham Hospital the incidence of rheumatic fever in the years 1914 to 1923 was 1.85 per cent of all medical admissions the clinical incidence of mitral stenosis was 3.89 per cent and the incidence of mitral stenosis in the autopsy room was 4.68 per cent while in New Orleans at the Charity Hospital these percentages from 1916 to 1923 were 0.03 0.08 and 0.23 respectively and in Baltimore at the Johns Hopkins Hospital from 1914 to 1922 0.73 2.01 and 1.30 respectively (Harrison and Levine 1924). This climatic difference has been so great that victims of the rheumatic infection have been advised sometimes to move from northern latitudes to southern and a few have done so. The reports from such a step have been in the main favorable (Coburn 1931 Jones White Roche Perdue and Ryan 1937) but it is to be noted that rheumatic heart disease has been discovered in recent years even in natives of tropical lands such as Cuba (Perez de los Reyes et al 1944) Puerto Rico (Francisco 1947) Panama (Hardgrove et al 1946) Curaçao (Hartz and Van der Sar 1946) and New Guinea (Levine 1946). Edstrom (1944) has even tried to influence the rheumatic infection by artificially producing it

tropical climate indoors in the temperate zone for long time treatment of active rheumatism with suggestive but not conclusive favorable results. The Rocky Mountain states harbor a considerable amount of rheumatic heart disease up to 27 per cent of all cardiac patients (Cannon, 1946) as was confirmed by military experience during World War II while the high plateau and perhaps even the lower lands also in Mexico have shown a surprisingly great number of rheumatic heart cases some 30 to 50 per cent of all cardiacs (Chavez 1942 Cortes and Villarreal 1947). It is likely that both prevalence of hemolytic streptococcus infection and overcrowded living quarters play an important role in these areas.

*Family incidence* One of the most interesting features of the rheumatic infection and of the rheumatic type of heart disease is their occurrence in different members of one family. Several studies have indicated that from 37 to 50 per cent at least of patients with rheumatic fever, chorea or rheumatic heart disease have near relatives with a history of similar trouble (as compared to a control series). Three factors are probably responsible for such family incidence: (1) inherited susceptibility to the rheumatic infection, (2) close contact with the actual spread of the exciting organism from one throat to another, and (3) crowded or unsanitary living conditions, sometimes with inadequate food and clothing.

*Social and economic status* An important factor in the occurrence of the rheumatic infection and of rheumatic heart disease appears to be the social and economic status of the individual. These diseases are much more common, by 100 per cent at least, among the crowded poor than among the well-to-do inhabitants of almost every community. In the large American private schools rheumatic fever, chorea, and rheumatic heart disease are infrequent while in the large public schools they are relatively common. Crowding, exposure to cold and wet without sufficient protection, malnutrition, and fatigue are probably all factors in producing this contrast.

*Epidemic form* Finally there is some evidence that at times under suitable conditions the rheumatic infection in the nature of rheumatic fever assumes an epidemic form. This was noted among the soldiers during World War I and infrequently among civilians since, and was encountered again in World War II. It may occur when an infecting organism of unusual virulence attacks a group of susceptible individuals exposed to adverse conditions such as bad weather and fatigue. It has been especially noted in groups of young people immediately following infection by a virulent hemolytic streptococcus in epidemic form: a certain number of susceptible individuals though a small percentage of the persons attacked by the original infection may develop rheumatic fever. In camp barracks and other living quarters of military personnel during World War II about 4 to 5 per cent of the young men exposed to and infected by the hemolytic streptococcus of various strains developed rheumatic fever some 10 to 15 days later; this was especially noted among the new recruits and in more crowded living conditions and in colder climates (Feasby 1944 and Barber 1946).

**Pathology** A generation ago endocarditis was the only well recognized common manifestation of rheumatic heart disease acute or chronic pericarditis was admitted as an occasional complication but little attention was paid to involvement of the myocardium or as a matter of fact to the widespread effects of the disease throughout the body Much advance in the proper understanding of this kind of heart disease has come in the last thirty years

The more severe the rheumatic infection in early youth the more extensive as a rule is the cardiac damage Once it was thought that only about two thirds of the attacks of rheumatic fever and about one third of those of chorea affected the heart but careful examination is now revealing a somewhat different incidence There was for example evidence of permanent cardiac damage in 86 per cent of 518 cases of rheumatic fever in 73 per cent of 348 cases of chorea and rheumatic fever and in 3 per cent of 134 cases of uncomplicated chorea analyzed at the House of the Good Samaritan in Boston (Jones and Bland 1935) Findings vary however as indicated by another series of 175 cases of acute rheumatic fever 50 per cent of whom showed no evidence of heart disease after follow up periods averaging seven years (Brown and Wolff 1940) Electrocardiographic and postmortem examinations have often shown myocardial and even slight endocardial involvement even though on physical examination there had been no sign whatsoever of heart disease It is probable that in every case of rheumatic infection there is some heart disease however slight or transient and that in a certain percentage of the total number there is complete recovery with return to normal or at least not sufficient deformity of valves or lesion of myocardium or pericardium to produce abnormal signs

The typical heart lesion of the rheumatic infection is an inflammatory reaction about the smaller arteries consisting of groups of small round mononuclear cells with a few giant cells (Aschoff 1904) this has been called the Aschoff body (Figure 82) and its discovery anywhere in the heart or pericardium has been considered almost pathognomonic of the activity of the rheumatic infection There may be but few of such lesions present or they may be widespread and in groups They apparently come and go leaving no trace unless the disease has been so extensive that nutrition has been interfered with and scar tissue results a sequela of more than slight fibrosis is very rare in the myocardium although a few instances have been recorded of rheumatic heart block remaining as a chronic state after it has appeared during the acute rheumatic infection

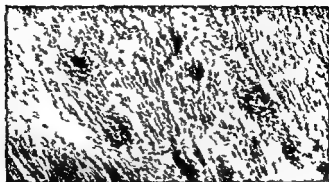
Aschoff L. Zur Myocarditisfrage *Verhandl d deutsch path Gesellschaft* 1904 VIII 46

Aschoff here gives the first clear description of the more or less specific rheumatic myocardial lesion which has been called by his name (Aschoff body) (The translation is by myself)

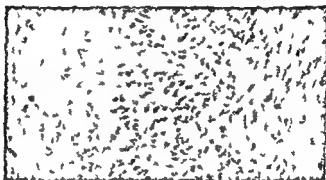
We have succeeded in establishing the histological structure of the myocardial reaction to the rheumatic infection by finding peculiar nodules which appear to be specific These nodules were indeed clearly defined in only two cases of recurrent endocarditis but in other cases cellular proliferations corresponded exactly in



A



B



C



FIG 82 Rheumatic myocarditis (A) Microphotograph showing typical Aschoff bodies in the (ventricular) heart muscle in acute rheumatic heart disease (Thalmer and Rothschild *J Exper Med* 1914 XIX 417)

(B) Microphotograph (higher power) of myocardium of child dying of severe rheumatic infection showing extensive destruction of the muscle cells with invasion by leukocytes and a few multinucleated giant cells (kindness of the House of the Good Samaritan Boston)

(C) Microphotograph of myocardium from case dying of severe recurrent rheumatism. There is evident at the left old fibrotic change from a previous rheumatic infection, and at the right new necrotic and hemorrhagic lesions due to the recurrent rheumatism (kindness of the House of the Good Samaritan Boston)

their locations to the lesions of these two hearts. They were regularly situated in the neighborhood of the small and medium sized blood vessels and often showed the closest relationship to the adventitia of these vessels. There even was found a disease of all the vessel walls somewhat comparable to that described for arteritis nodosa. The above mentioned nodules are extraordinarily small, highly submiliary and are comprised of collections of unusually large cells with one or more abnormally large, slightly notched or polymorphic nuclei. The grouping of cells often occurs in the form of a fan or a rosette. The periphery of the nodule is composed of the large nucleated cells and the center often of an apparently weakly staining necrotic mass of coalescent cellular protoplasm. With careful observation the fan-shaped foci remind one of the smallest necrotic areas with cellular periphery which one finds so often in gouty kidneys. In the rheumatic nodules one has to do not with the tubercular or foreign body giant cells with several regularly formed nuclei but with structures which resemble rather the large nucleated cells in certain sarcomas or in pseudoleukemic proliferations. On the other hand the nodules are not composed solely of such large nucleated cells but small and large lymphocytes and also polymorphonuclear leukocytes are wedged in between the large cells at least at the periphery or else themselves comprise an outer zone from which irregular stray cells extend out further into the connective tissue interspaces. In these outer areas there can still be found single large nucleated cells and all gradations down to simple large leukocytic elements which are more or less commonly found in the neighborhood of the smallest vessels in all inflammatory reactions. These leukocytic elements are the large cells which Hayem and Romberg have described but whose origin remained doubtful in their minds. Out of these large cells which are the adventitial cells of the blood vessels swollen by inflammatory reaction the large nucleated giant like cells are formed which single or collected in nodules give to the rheumatic proliferations a characteristic stamp. It should further be observed that the number of eosinophilic cells in these nodules is very small.

Years later it was demonstrated that the Aschoff body is not the earliest tissue change in the rheumatic infection but often is a rather late reaction, probably a part of the process of recovery and repair (Coburn 1933). The earliest tissue changes are those of destruction (necrosis) and a tendency to hemorrhage throughout the body, especially well marked in the more severe cases. The myocardium particularly is involved and may be so seriously damaged in the sicker children that the heart dilates acutely or subacutely. Such dilatation of the heart may lead to death from heart failure or to more or less permanent cardiac enlargement or it may be followed by good recovery with more or less complete return of the heart to normal size. The recognition of this fact is of the greatest importance in the proper understanding of the cardiac symptoms and signs in the course of the acute and subacute rheumatic infection in the analysis of the late after-effects and in rational prognosis and treatment.

The typical rheumatic endocarditis consists of a so-called verrucous inflammatory reaction, tiny vegetations of thrombotic nature composed chiefly of fibrin and tending particularly to appear in a row on the atrial surface of the mitral and tricuspid valve cusps and on the ventricular surface of the semilunar valve cusps (Figure 83) at the line of closure, not at the edge, although

sometimes they are distributed elsewhere over the cusps. The exact pathogenesis of these thrombi or of the damaged areas of the endocardium on which the thrombus formation takes place is not known whether due to direct toxic action of the blood stream or via the blood vessels in the valves or to local allergic reaction to agent or agents in the blood (manufactured elsewhere). In any event the slight trauma caused by valve closure appears of some importance in favoring the appearance of the earliest lesions. In fact nonrheumatic



FIG. 83. Photograph showing acute and chronic rheumatic endocarditis of the aortic valve. Note the vegetations along the line of closure, adhesions of the cusps to produce slight aortic stenosis, scarring of the endocardium below the valve, and thickening of the chordae tendineae of the mitral valve. The patient was a boy 14 years old. (Kindness of Dr. Ronald Grant, Guy's Hospital, London.)

bland thrombi of small size very probably are deposited on the lines of closure of the heart valves especially the mitral on occasion almost as a normal event the result of a variety of influences they may do no serious harm but can quite likely result in a slight chronic thickening of the valve edge which may justifiably or not arouse suspicion of a rheumatic etiology Besides the involvement of valve cusps there is commonly in rheumatic endocarditis especially of the severe type inflammation of the chordae tendineae and of the wall of ventricle or atrium especially of the left atrium just above the valve this results in scarring and in the case of the chordae in thickening shortening and coalescence to add to the valve deformity

Rheumatic pericarditis consists of a fibrinous or a serofibrinous reaction more or less extensive sometimes giving rise to the typical bread and butter appearance (as shown in Figure 134 page 710) but rarely to large effusions (a typical serous exudate rarely bloody) In healing small or large scars are left with or without localized or complete adhesions and only rarely with any important external adhesions Constrictive pericarditis of sufficient degree to cause symptoms or signs (Pick's disease) has not been encountered once in 1 000 cases of the rheumatic infection many with pericarditis followed over a ten to twenty year period at the House of the Good Samaritan in Boston (Jones and Bland 1942) nor has any one of 53 cases of chronic constrictive pericarditis examined by myself had a rheumatic etiology although two among them had coincidental rheumatic valvular disease

When as frequently happens myocardium endocardium and pericardium are all involved we speak of *pancarditis* and now and then especially in young children such pancarditis may be very severe and overwhelming resulting in early death from heart failure

Furthermore the rheumatic infection may attack other organs beside the heart, pericardium joints and brain (chorea) The arteries—aorta pulmonary artery and smaller visceral and peripheral vessels—the lungs the pleurae the diaphragm and the peritoneum may be involved by hemorrhages or by lesions resembling the Aschoff body sometimes with serious consequences An important and interesting pulmonary rheumatic lesion in severe cases is the hemorrhagic consolidation sometimes labeled erroneously rheumatic pneumonia this lesion quickly comes and goes

The rheumatic infection is typically a slow one and recurrent a fresh invasion of the heart is common on top of healed lesions of valves or of atrial or ventricular endocardium of chordae tendineae or of pericardium

The infection may clear up in some cases as stated above with little or no trace but commonly a scarring of the endocardium is made evident by valvular deformity Chronic pericardial damage sometimes persists in the nature of adhesions of varying extent and importance Rarely there is a residual myocardial lesion as shown by permanent heart block or ventricular dilatation A discussion of the particular valve lesions of pericarditis and of heart block will be found in Parts III and IV of this book Suffice it to say here that there is a very wide variation of cardiac damage resulting from the rheumatic infec

tion and constituting chronic rheumatic heart disease not only with respect to the particular parts of the heart involved but also with respect to the degree of involvement

It should be added that chronic cardiac dilatation accompanying valvular defects or pericardial adhesions may be due as much or more to the rheumatic infection of the myocardium as to the particular valvular handicaps that cause heart strain. Indeed it may be conjectured that in rare cases cardiac enlargement even of high degree and leading to failure may be due to an old severe antecedent rheumatic involvement of the myocardium with little or no endocardial or pericardial scarring. This is an explanation of some of the cases of heart disease of unknown origin which appeals to one as logical but which as yet lacks proof.

**Symptoms** The symptoms of rheumatic heart disease depend upon three factors: (1) activity of the rheumatic infection, (2) obstruction to the circulation resulting from the specific lesions, and (3) heart failure which may come as the result of overwhelming acute or subacute myocarditis or of chronic valvular disease or of disturbed heart rhythm or of two or even all three of these conditions combined. Many persons with chronic rheumatic heart disease have no symptoms at all and live active lives without difficulty. Of greater immediate importance than study of the structural defects is the determination of the presence or absence of activity of the rheumatic infection.

The symptoms of acute or subacute rheumatic infection include those of any infection but depend also on the reaction of the individual patient to the causative agent. Joint pain, tenderness, swelling, heat, and redness, muscle aching, chorea (rarely combined with joint symptoms), fever, chills (rarely), sweating (sometimes profuse), weakness, effort syndrome, malaise, anorexia, epistaxis (occasionally), and loss of color and weight are all symptoms of the active rheumatic infection. Their severity varies with the virulence of the infection and the resistance of the patient. They may be mild and hardly noticeable—merely slight fever and malaise with or without muscle or joint soreness—and not always sufficient to cause the victim to stop school or work or to induce the family to consult a physician unless they have been educated by previous experience or are aware of the likelihood of involvement of the heart. In rare cases of rheumatic fever there may be abdominal pain simulating that of or actually due to an acute appendicitis. A low grade rheumatic heart infection, ordinarily called subacute rheumatic carditis, may set in and last for weeks or months or even years, especially in children, showing itself only by a loss of energy and by the appearance of ill health and of a slight elevation of temperature at intervals or daily (99° F or a little more by mouth or 100° F by rectum). Such a situation is very common while a virulent polyarthritis in children is relatively rare. A severe short attack of rheumatic fever with extreme joint involvement and little or no heart disease is much more likely to occur in the adult. Years ago it was a common though by no means invariable rule that the older the individual the more the joints suffered and the less the heart; the younger the subject the more the heart suffered and

the less the joints. In recent years on the other hand a fulminating poly-articular rheumatism is rarely seen in any age even in New England this is apparently due to a spontaneous change in the virulence or character of the rheumatic infection itself though the common and early use of the salicylates (especially aspirin) for any illness by the populace at large may also have a modifying and misleading influence on the acute rheumatic process.

*The heart itself when acutely invaded* by the rheumatic infection only occasionally causes symptoms. Sometimes it may ache so that precordial discomfort is felt sometimes there are sharp pains in the chest although they are not common rarely there is actual angina pectoris occurring usually in subacute or chronic valvular disease with marked aortic regurgitation probably dependent on insufficient coronary blood supply due not only to low diastolic blood pressure but also to a storm of vasoconstriction involving the coronary arteries and producing transient hypertension in a sensitive individual. Infrequently disturbances of rhythm occur such as premature beats or paroxysmal tachycardia giving rise to palpitation usually the palpitation that may be felt is but a part of the effort syndrome that accompanies any infection. Dyspnea also is usually due to effort syndrome but sometimes it arises from an acute pericarditis or from cardiac dilatation and failure accompanying an overwhelming acute myocarditis. When the heart fails during the acute rheumatic infection in childhood it is a total heart failure with little or no dyspnea but with congestion behind the right ventricle giving rise on occasion to upper abdominal discomfort from engorgement of liver and other abdominal viscera.

*The chronic rheumatic heart* frequently fails from the strain of valvular disease complicated by a disturbing arrhythmia (especially atrial fibrillation) or by an acute infection (rheumatic or nonrheumatic) then appear the typical symptoms of congestive failure (see Chapter 30). Angina pectoris may occur with marked aortic stenosis or regurgitation but rarely with other valve defect. Also without actual failure the obstruction due to mitral stenosis may occasion congestion of the lungs with dyspnea cough hemoptysis or it may rarely cause hoarseness from laryngeal paralysis. At times the obstruction due to tricuspid stenosis may block the return of blood into the right ventricle and left heart chambers with resulting congestion of liver and large veins similar to the condition found in cases of chronic constrictive pericarditis (so-called Pick's disease).

The symptoms of an active rheumatic infection may frequently be superimposed on those of chronic rheumatic heart disease when there is a recurrent rheumatic attack in fact heart failure in chronic rheumatic heart disease is often precipitated by the new infection or is due more to its presence than to the old lesion.

*Signs.* The signs of rheumatic heart disease are dependent on the factors of activity of the infection of the strength of the heart and of the particular lesions. There may be nothing but slight enlargement of the heart with a systolic murmur at the apex or a slight diastolic murmur along the left border

of the sternum found on routine examination there may be an enormously enlarged heart with several murmurs absolute arrhythmia and marked congestive failure or there may be any combination of signs between these two extremes. Commonly in the child there is slight to moderate cardiac enlargement with normal rhythm moderate systolic and middiastolic murmurs at the apex (the result of left ventricular dilatation during the course of the first rheumatic infection and later on, of mitral valve disease itself) and sometimes a diastolic blow (of aortic regurgitation) along the left border of the sternum without frank congestive heart failure but frequently with slight fever due to activity of the rheumatic infection. It is a common experience to note the disappearance of the physical signs of rheumatic heart disease (enlargement, systolic murmur and even mitral diastolic murmur) when cardiac dilatation subsides along with the active rheumatic infection (Bland Jones and White 1936) these signs especially the mitral diastolic murmur used to be attributed to chronic heart disease but now it is realized that usually an interval of several years is necessary for the establishment of structural mitral stenosis. Commonly in the adult on the other hand especially in the female there is a well marked apical diastolic murmur of mitral stenosis, absolute arrhythmia of atrial fibrillation and very limited cardiac reserve or slight to moderate congestive failure with or without aortic regurgitation in the adult male one finds somewhat more often a preponderant or even seemingly isolated aortic valve lesion (stenosis, regurgitation or both) with normal rhythm. Although these findings are the most common they may be replaced by others. The signs of the particular valve defects will be discussed in Part III.

The more severe cases of active rheumatic infection may show also frank congestive heart failure which in childhood involves the whole heart with resultant systemic venous congestion (big liver and dependent edema including the face with the child lying flat) rather than pulmonary congestion due to primary left heart failure (Walsh and Sprague 1941).

Infrequently one finds in acute rheumatism two additional signs which are subcutaneous and cutaneous manifestations rheumatic nodules and skin lesions.

Rheumatic nodules are important signs of a severe rheumatic infection their presence indicates that the infection is still active even though they persist or recur for many months. These nodules vary in size number location and with the severity of the disease. Usually of pinhead to pea size and shape rarely as large as Lima beans they are found most commonly subcutaneously and are loosely attached to tendon sheath periosteum or joint capsule over elbows knees ankles skull fingers wrists toes and shoulders in frequency in about the order named and usually more or less symmetrically on the two sides of the body (Figure 84). When very extensive they may be found scattered over the entire head thorax and long bones. In number they vary from two or three a common finding to one hundred or more very rarely. They tend to come and go singly or in crops each one lasting for a few days or weeks they may not completely disappear for months. In some parts of the

world they are more common than in others but this variation is probably due mainly to the severity of the infection. Their incidence has extended from 2 or 3 per cent to over 75 per cent in different groups of patients with acute rheumatic infections in different communities. They are less commonly seen nowadays in New England than they were two or three decades ago perhaps paralleling the decrease in the severity of the disease itself.

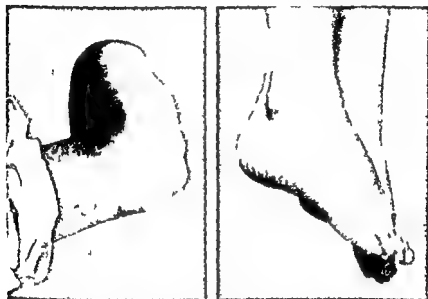


FIG. 11. Photograph showing joints of child with rheumatic nodules on elbow, ankle and foot. Note nodule also on the tendo Achillis. (Kindness of the Cardiac Clinic, Children's Hospital, Boston.)

Erythema multiforme (marginatum) is the commonest of the cutaneous signs accompanying the rheumatic infection, occurring in about 15 per cent of the cases at some time or other, tending to recur over periods of a few weeks or months and to appear in patients who have had or who later develop rheumatic nodules. Erythema nodosum, urticaria, and angioneurotic edema are relatively rare. Purpura rheumatica and petechial hemorrhages are sometimes found. Petechiae may be readily produced in the skin of subjects with an acute or subacute rheumatic infection by pressure, as with a blood pressure cuff; this is due to the tendency to bleed which is a part of rheumatic fever as well as of bacterial endocarditis.

Other occasional signs of severe rheumatic infection are those of acute pleuritis, acute pericarditis, or both, fibrinous or with effusion, and sometimes hemorrhagic pulmonary disease (areas of hemorrhagic consolidation) which are apparently of rheumatic origin and as a rule rapid in their appearance and disappearance. Chronic adhesive pericarditis may show itself in the recovered cases but often it gives no clear sign. This will be further discussed in Part III of this book.



The results of all other methods of examination of an individual with rheumatic heart disease are likewise dependent on the three factors of activity of infection cardiac insufficiency, and the particular structural lesion. Commonly it is the presence of mitral valve disease and of stenosis of that valve that accounts for the findings in chronic cases.

The blood pressure is normal or low unless there is a complicating essential hypertension, thyrotoxicosis, or considerable aortic regurgitation. The pulse and pulse pressure are very full when there is marked aortic regurgitation, small when there is considerable mitral stenosis, and very small when there is pronounced aortic stenosis.

Roentgenologic study is of help in following a case of rheumatic heart disease. In the acute infection and early stages of organic involvement the heart shadow may be normal or it may reveal enlargement and change in shape of the heart shadow due most often to more or less acute dilatation of the heart (Figure 85) or less commonly to accumulation of fluid in the pericardium in rheumatic pericarditis or to both of these conditions. In chronic cases it shows various typical changes of shape and size when there are well marked chronic valvular lesions (see Chapter 26).

The electrocardiogram may be normal in rheumatic heart disease except for a rapid rate (sinoatrial tachycardia) which is found frequently, but if many serial records are taken of any case abnormalities are commonly found though often in but a few records. When the electrocardiogram is abnormal it may show either an arrhythmia, delay in conduction between atria and ventricles, abnormal *T* waves, intraventricular block, or abnormal axis deviation. The rhythm is absolutely irregular in more than half of the adult cases with marked mitral stenosis, but it is generally normal or disturbed only by premature beats in aortic valve disease, pericarditis, or preponderant mitral regurgitation. Slight grades of heart block as shown by *P-R* intervals of 0.21 or 0.22 second are common during the acute rheumatic infection (Figure 86) and even *P-R* interval prolongation to 0.25 second, dropped beats, or higher grades of block are occasionally seen. This finding of block may be the only sign of cardiac involvement and it has been noted in rare cases as the first evidence of the rheumatic infection in the body, polyarthritis developing shortly afterward (White 1916). Also in very rare cases the heart block during the active infection may progress to such a high degree that Adams Stokes attacks occur for a short time. As a rule the heart block clears up when the rheumatic infection subsides, but a few instances of permanent rheumatic heart block have been noted and it has also been observed that rheumatic heart cases with a persistently prolonged *P-R* interval are more likely to develop atrial fibrillation than are those whose *P-R* interval is normal due in part it is suggested to vagal action (Bruenn 1937, Altschule 1939). It is important to note moreover that prolongation and variability of the *P-R* interval can occur in normal children as well as in rheumatic children without evidence of rheumatic activity (Reyersbach and Kuttner 1940).

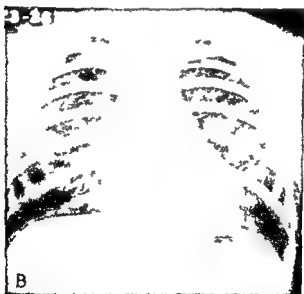
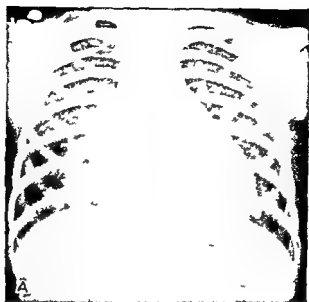


FIG 85 Roentgenograms showing (A) considerable dilatation of the heart in a young girl during acute rheumatic fever and (B) reduction in heart size several months later after complete subsidence of the infection. At the time the first record was taken there were systolic and middiastolic murmurs at the apex which disappeared when the dilatation subsided. There was no evidence of acute pericarditis. Note the rather localized pulmonary edema in the right lung in (A). The transverse diameter of the heart in (A) was 11.6 cm and in (B) 10.4 cm.

In addition to the delay in atrioventricular conduction slight deformities of the *QRS* and *T* waves or of the *S-T* segment are occasionally noted during the acute and subacute infection and may represent slight transient intra ventricular block myocarditis and pericarditis, rarely they may persist. In a few cases of chronic rheumatic heart disease particularly with mitral stenosis bundle branch block of the right type with wide *S*<sub>1</sub> or *QS*<sub>1</sub> may be

Lead

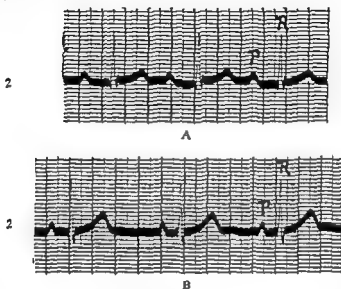


FIG 86 Electrocardiograms showing Lead 2 in (A) during acute rheumatic fever Dec 17 1935 and in (B) two weeks later during convalescence Jan 2 1936. Note the prolonged *P R* interval (0.25 second) in (A) and normal *P R* interval (0.17 second) in (B). Boy 13 years old. Time = 0.1 and 0.2 second.

found. Finally it is common to find abnormal axis deviation and ventricular preponderance in chronic valvular disease if either mitral stenosis or aortic regurgitation is preponderant and of marked degree. Right axis deviation occurring with the former and left axis deviation with the latter. Absence of abnormal axis deviation by no means rules out either valvular lesion. In fact high degrees of both may be present in the same case with normal electric axis deviation. The effect of involvement of one of the valves neutralizing the effect of involvement of the other in the classical limb leads, but the precordial leads reveal the enlargement of both ventricles. A very interesting electrocardiographic finding occasionally seen in acute rheumatic fever with congestive heart failure is a shift of the electric axis to the right due doubtless in large part to the acute right ventricular dilatation (more marked than that on the left side) which decreases or disappears with the patient's improvement or recovery (Walsh and Sprague 1941). Prolongation of the *Q T* time has been reported in rheumatic fever but it is not a consistent finding and may be due to other factors (e.g. cardiac enlargement) rather than to the rheumatic fever itself.

Blood and urine are frequently abnormal when there is an active rheumatic or complicating infection or congestive failure. A leukocytosis of 10 000 or over often but not always accompanies acute rheumatic heart disease the severer the infection the higher the white count but it rarely passes 20 000. A slight or even moderately severe hypochromic anemia is common in children with active rheumatic heart disease. The sedimentation rate of the blood is usually increased in proportion to the activity of the rheumatic disease and may be the only evidence that persists of a long-drawn out low grade infection. The blood culture is usually negative. A positive skin reaction has been reported as a frequent finding when the toxic filtrate of the hemolytic streptococcus (or its nucleoprotein) is injected intradermally in patients who have had rheumatic fever but this has been found to be a non-specific reaction that is it occurs also in cases who have had *Streptococcus hemolyticus* infections without rheumatic fever. Albuminuria is the usual finding during congestive heart failure and during moderate or high fever in the acute rheumatic infection. Occasional red blood corpuscles are frequently found in the urinary sediment during the active infection.

**Course and prognosis** Rheumatic heart disease begins with an acute invasion of the heart generally in childhood between the ages of 4 and 12 years. Instances of very early infection are on record even in the fetus and in the nursing infant whose mothers had rheumatic fever at the time. On the other hand the rheumatic infection and resulting heart disease have sometimes occurred first in adult life. Initial attacks of rheumatic fever have been reported in six patients over 60 years of age (Ferris and Myers 1935). I have myself encountered cases with recurrent attacks at 66 and at 72 years of age. The earlier in life the cardiac involvement the more serious it is likely to be and the shorter the patient's life. It is usual for the child to survive the first rheumatic infection whether it is frank rheumatic fever chorea ill-defined sickness or rheumatic heart infection alone. Although this earliest infection is often mild it may last for months or years and leave a badly crippled heart. Recurrent infections throughout childhood may cause death by heart failure by the toxic effect of the disease itself or by complications. But usually there is survival in spite of one two three or more fresh attacks or exacerbations of rheumatism in childhood and youth the victim showing a variable amount of permanent heart damage by the time he reaches the age of 20 years. Rarely does he escape unscathed unless he has had but one or at most two slight attacks of rheumatism. The greater the number of recurrences of the infection the greater is the heart damage. In adult life he runs far less risk from new rheumatic attacks but on the other hand he runs three other risks (1) atrial fibrillation (2) congestive heart failure and (3) subacute bacterial (*Streptococcus viridans*) endocarditis. The first of these complications (atrial fibrillation) is common in the case of well marked mitral stenosis but it is relatively rare in all other cases. The second (congestive failure) is likely to occur in any severely damaged heart when there is aortic or mitral valve disease uncontrolled tachycardia (especially in atrial fibrillation).

infection rheumatic or otherwise which adds appreciably to the strain. The third (subacute bacterial endocarditis) is commonest in aortic valve disease or with mitral lesions in which stenosis is not marked that is when regurgitation predominates so it is most common in just that type of chronic rheumatic heart disease which atrial fibrillation and congestive failure are not likely to accompany but why this should be so we do not yet know.

Death from heart failure or complicating infection commonly overtakes the victim of rheumatic heart disease in the second fourth or fifth decade of life after many years usually ten to twenty of partial crippling and restriction of activity and after a few years usually two to five of partial or complete invalidism. Sometimes however if the lesions are but slight and the subject is careful fortunate or both he may survive to old age and die a noncardiac death. Slight mitral stenosis or regurgitation slight aortic stenosis or regurgitation and a noncrippling adhesive pericarditis are all lesions that are well borne with respect both to duration and to activity of life but in general the mitral valve lesions are better borne than the aortic. A ten year follow up of 506 cases with rheumatic valvular lesions gave a relative mortality of 3.7 per cent for mitral insufficiency, 12.5 per cent for mitral stenosis and 37.4 per cent for aortic valve lesions with or without mitral valve involvement (Svartz and Ernberg 1947). In Texas Fashena (1944) found the death rate from rheumatic fever in the school age period to be not very different from that in New England or in the United States as a whole. Cases of mitral stenosis surviving the age of 80 years are now on record (White and Bland 1941). Wilson and Lubschez (1948) have presented some interesting data as to longevity based on a thirty year period of observation of 1,042 children who had rheumatic fever. The mean age at onset of their rheumatism was 6.5 years. The average length of observation was 14.8 years among 226 deaths. 75.7 per cent were due to rheumatic disease of the heart and 10.2 per cent to subacute bacterial endocarditis. They concluded that an affected child has 4 chances out of 5 to survive childhood, 3 out of 4 to survive puberty and then 19 chances out of 20 to survive early adult life, with an overall chance of 1 out of 2 to survive the age of 40 years.

**Complications.** The three most important complications of rheumatic heart disease have been mentioned above: (1) atrial fibrillation which complicates two thirds of the cases of considerable mitral stenosis and about one fifth of all cases of chronic rheumatic heart disease (17.5 per cent of the 956 cases of White and Jones series); (2) congestive heart failure which eventually complicates at least two thirds of all cases; and (3) subacute bacterial (*Streptococcus viridans*) endocarditis which attacks one in every 4 to 20 cases (2.5 to 5 per cent) of rheumatic heart involvement. Jones and Bland (1942) have found subacute bacterial endocarditis in 16 (7.9 per cent) of 203 fatal cases of rheumatic fever or rheumatic heart disease while Gelfman (1943) has reported the finding of such involvement in 25 per cent of autopsied cases of rheumatic heart disease in two Boston hospitals. The most common or important complications are congestive heart failure, atrial fibrillation, and subacute bacterial endocarditis.

of White and Jones

series) essential hypertension (also in 2 per cent of White and Jones series) syphilitic aortitis congenital defects thyrotoxicosis and emphysema (each of which last named conditions complicated less than 1 per cent of White and Jones series) Neurocirculatory asthenia frequently is found in varying degree in the victim of rheumatic heart disease it was well marked in 37 of the 956 cases (4 per cent) of the series noted above (White and Jones) Mild and serious infections of all sorts nephritis pulmonary disease nervous diseases and lesions of the gastrointestinal tract may complicate rheumatic heart disease but it is of interest to note that glomerulonephritis rarely accompanies rheumatic fever itself (Baehr and Schiffrin 1931) The relative infrequency of pulmonary tuberculosis in cases of well marked mitral stenosis has been pointed out it has been suggested that the chronic pulmonary stasis in mitral stenosis protects the lungs from tuberculosis

Four complications of rheumatic heart disease are largely dependent on the mitral stenosis or congestive failure that may be present The commonest is pulmonary embolism which may arise in dilated right heart chambers but most often comes from thrombosed veins in legs resulting largely from the venous stasis secondary to the heart trouble Embolism to brain or elsewhere may result from thrombosis in the left atrium Acute pulmonary congestion producing edema or hemoptysis may come from increased pressure in the pulmonary circulation due to mitral stenosis especially when there is a rapid heart rate Rarely hoarseness may result from left recurrent laryngeal paralysis

Another rare complication namely that of angina pectoris may attend rheumatic heart disease it was found in 13 of White and Jones series of 956 cases the 5 older cases having coronary disease and the 8 younger ones marked aortic regurgitation Angina pectoris may also very rarely complicate mitral stenosis in young people (Hochrein 1930)

Of disturbances of rhythm atrial fibrillation and heart block have been discussed Atrial flutter is rare generally complicating mitral stenosis Paroxysmal tachycardia (regular) is common but less frequent than atrial fibrillation The presence of sinus arrhythmia although somewhat favorable is of little aid in the judgment of a case since it does not indicate that the heart is normal and since it does not prove that a low grade active infection is no longer in progress as was once thought

**Treatment** No treatment for rheumatic heart disease per se is needed unless one or more of the important complications are present—infection atrial fibrillation or flutter or congestive failure The treatment of the arrhythmias and of congestive failure is discussed in Part IV of this book In prevention of acute rheumatism either in first or in recurrent attacks the most important measure is the avoidance of upper respiratory infections or the early and adequate use of penicillin if the hemolytic streptococcus is the offending agent Although helpful it is not essential to enlist the aid of a mild climate for children have been kept well even in open air sanatoria in the north in the winter by practical exclusion of infected contacts (Hubbard and Griffin 1940)

If acute or subacute rheumatic infection is present *rest in bed*, a light simple diet with adequate vitamins and appropriate therapy directed against the infection are indicated. Usually *good nursing care* is of prime importance and worth more than most drugs. Satisfactory gain in weight is a good indication of the favorable progress of convalescence but it is not a sign of cure.

In the third edition of this book it was stated that for the rheumatic infection itself no specific therapy has as yet been established although much reliance has been placed by some on the *salicylates* which without any question have a well nigh specific effect in the rapid control of fever, joint swelling and pain in rheumatic fever for which purpose they may be freely used. It is possible also though not proved that salicylate therapy may help to effect a rapid absorption of rheumatic pericardial and pleural exudate and effusion. Since that time hormone therapy of arthritis and certain other diseases including rheumatic fever, has been introduced which may or may not prove to be specific or very near it.

*Hormone therapy* The application of ACTH (adrenocorticotrophic hormone) to acute rheumatic fever has been tried recently with surprising immediate success in the majority of cases for example seven patients at the House of the Good Samaritan in Boston given 10 to 25 mg of ACTH four times a day for four to six weeks have all responded favorably. As a rule their temperature has been reduced to normal in two to three days their sedimentation rates have become normal in two weeks and even those seriously ill with congestive failure have improved greatly although they still may need other treatment for the congestion itself. Cortisone also has been found to be effective in suppressing the disease (Hench et al., 1950). These preliminary observations of course need further confirmation and more prolonged follow up.

*Salicylate therapy* A dose of 15 to 30 gr (1 to 2 gm) of sodium salicylate with an equal amount of sodium bicarbonate every two to four hours until relief of symptoms and of fever or a toxic reaction (tinnitus, nausea, vomiting, urticaria) has ensued is sometimes recommended with great benefit in this way even 150 to 240 gr (10 to 16 gm) may be administered in a single day. Rarely is it necessary or possible to continue such a large dosage for more than a few days. For children the dosage of salicylate may be halved and for infants one fifth to one tenth of the amount given to adults should suffice but of course this medicine will rarely be needed at such an early age.

Intravenous salicylate therapy in large dosage has been tried out controlled by testing the concentration of the drug in the blood (Coburn, 1944), but its early promise like the saturation by oral salicylates a good many years ago has not been confirmed. Thus the statements made in the previous editions of this book still hold namely that the antipyretic effect of salicylates if constantly given may conceivably be harmful by masking some of the evidences of activity of the infection and so misleading one into a false sense of security and that if salicylates are used they should be employed only for symptoms of discomfort due to exudative reactions to the disease and occasionally

omitted for a few days at a time to determine the true course of the disease (temperature leukocyte count and signs and symptoms) However in the course of the trial of intravenous salicylate therapy a useful test for blood salicylate content was devised It has been demonstrated incidentally that as high a blood concentration of salicylate can be secured by oral administration as by intravenous Finally a warning is due as to the toxic effects of salicylate poisoning including a tendency to bleed and even delirium—such toxicity is more readily produced by intravenous administration

*Vitamin C therapy* Apparently midway between the effects of ACTH and salicylates is that of massive doses of vitamin C the favorable effect of which has recently been described by Massell et al 1950 Acute rheumatic involvement has been controlled in a series of cases by the administration of 1 gm of vitamin C in orange or apple juice four times a day The exact mechanism by which this effect is produced is still obscure

No place has been found for antihistaminic drug therapy in rheumatic fever despite the common supposition that this disease may be related to the allergies

Serum treatment of the acute rheumatic infection whether or not the infection involves the heart has never evolved from the experimental stage The use of specific monovalent or polyvalent streptococcus vaccines has also been suggested and tried but further study is needed before definite conclusions can be reached A possible success of such therapy is to be ascribed rather to the reduction of streptococcus infections which may excite the rheumatic infection than to the primary control of the rheumatic infection itself

A much more important prophylactic measure recently introduced that bids fair to reduce the incidence of the rheumatic infection in initial and especially in recurrent attacks has been first the administration of sulfonamide drugs in small dosage routinely throughout the winter and spring to susceptible children (e g 10 to 13 gm 15 to 20 gr sulfanilamide divided into 2 or 3 doses daily to a child of 8 years) to ward off or in larger dosage to treat the hemolytic streptococcus infections that so often precipitate active rheumatism and heart disease (Thomas et al 1939 1941 1942 Coburn 1941 Hansen et al 1942 and Kuttner and Reyersbach 1943) and more promising still of late the use of penicillin especially at the time of exposure to a streptococcus sore throat or when such is just beginning (Maliner and Amsterdam 1947 Goerner et al 1947 Milzer et al 1948 Massell et al 1948 Denny et al 1950) A daily oral dose of 100 000 to 300 000 units of penicillin has been found apparently effective (Pitt Evans 1950 Massell personal communication 1950) Similar preventive medicine may hopefully be practiced during acute infections or operative procedures (especially dental extractions) in the case of individuals with chronic rheumatic heart disease to ward off subacute bacterial endocarditis We still await however the final word as to the efficacy of these drugs in the prevention both of rheumatic fever and of subacute bacterial endocarditis



It is to be noted that neither penicillin nor streptomycin nor the sulfonamides have any favorable influence on the rheumatic process per se in fact the two latter may cause harm by their toxic effect

The *treatment of chorea* has been no more satisfactory than that of rheumatic fever. Absolute rest and quiet, with good nursing care are more effective than any other measures. Neither arsenic (e.g. Fowler's solution) nor the salicylates nor other drugs or serum appear to have any specific action in controlling chorea except for a promising recent experience with hormonal therapy (adrenocorticotrophic hormone). For very severe (convulsive) chorea magnesium sulfate intramuscularly, intravenously or intraspinally (in 25 per cent solution) has been reported to have a sedative effect. Phenobarbital (Luminal) barbital (Veronal) or other mild sedatives, tincture of stramonium and continuous baths have also been recommended. Febrile therapy by the use of foreign protein such as typhoid vaccine has also been used but this as a matter of fact may do harm by inciting an attack of rheumatic fever (Bland and Jones 1935).

The *convalescent care* of patients suffering from subacute rheumatic infections long continued and lasting for weeks, months or even years has been a problem attracting much attention in recent years. It is generally agreed that the active stage of the infection should be treated by rest in bed but there comes a time when it is difficult or impossible to be sure whether or not the infection has completely subsided. In the case of restless children who feel well enough to run about and whose control is difficult at home much discretion must be used for such cases institutional care where the discipline is good or supervision by able nurses may be essential during the active stage of the infection. When with the patient at rest in bed and not taking salicylates the temperature no longer rises over 99° F by mouth or 100° F by rectum the leukocyte count remains below 9 000 the sedimentation rate becomes normal the pulse rate keeps under 100 symptoms and signs of infection have disappeared and the nutrition is improved convalescence may be considered to have begun. The further length of time after that during which rest in bed should be continued and the rapidity at which convalescence should be allowed to proceed to full normal activity should not be determined by any set rule (some have been suggested) but by the conditions in the individual case. After severe infection a minimum of several months of convalescence should be prescribed before return to normal activity during this period a foster home or preferably the child's own home should be utilized with training of the family to cope properly with the situation.

Removal of the patient to a *tropical climate* for example Puerto Rico (Coburn 1931) or southern Florida (our own experience Jones White Roche Perdue and Ryan 1931 to 1936 inclusive reported in 1937) from the north during the colder seasons has been found generally to act favorably in restoring health to children who show an active rheumatic state although beneficial as a rule it cannot be regarded as specific and it is an expensive

procedure often not justifiable. Permanent residence in the tropics is preferable if a rheumatic family can readily arrange it.

During convalescence massage and then the simple exercises of walking, lifting and carrying will help to restore normal circulation and muscle function in the extremities. Special graded exercises are not necessary if common sense is used. Of great help in many cases has been recreational and even occupational therapy during convalescence and during the acute infectious stage. Membership in the In Bed Club for Children developed by Edith Terry of the Massachusetts General Hospital has greatly aided the morale of many hundreds of youngsters and their families.

*Tonsillectomy* is advisable in many patients with chronic rheumatic heart disease provided their tonsils are infected or abnormally large and provided their hearts are in satisfactory condition to stand the operation as they usually are. It is also to be recommended in many cases following active rheumatic infection after convalescence is well established. It has been advised and carried out even during the acute stage of the infection apparently sometimes with immediate benefit but certainly sometimes with exacerbation of trouble. This procedure is not to be recommended in most cases during the active process. The prophylactic effect of routine tonsil removal in the case of rheumatic infection (rheumatic fever, chorea, heart disease) has however been disappointing; there has been only slight evidence that it protects against either initial or recurrent attacks. If the tonsils are however infected or enlarged or if there are repeated attacks of tonsillitis, complete tonsillectomy should certainly be done. In such cases it is undoubtedly beneficial in the long run. The adenoid tissue in the nasopharynx should be removed with the tonsils. If the operation is done in very young children it usually has to be repeated after some years because of the new growth of lymphoid tissue in the pharynx.

Roentgen irradiation of the heart has also been tried in the therapy of active rheumatic infection (acute endocarditis and myocarditis) but its value has not been confirmed.

Surgical treatment of chronic rheumatic heart disease is limited to but very few cases. Despite the failure of mitral valvulotomy over 20 years ago, renewed attempts are underway at present to apply surgical therapy to valve defects but it is as yet too early to gauge the results or even to prophesy the various techniques that will be applied. Even plastic replacements have been suggested. One special condition due to rheumatic heart disease has however already been dramatically helped by surgery and that is recurrent pulmonary edema secondary to tight mitral stenosis. Three methods have been used which will be described in more detail in Chapter 26. They consist of (1) production of an atrial septal defect to relieve the high pressure in the left atrium and lungs, (2) more practically and effectively to anastomose a right pulmonary vein to the vena azygos major and (3) probably best of all, the surgical separation at their commissures of the adherent cusps of the mitral valve.

For acute pericardial effusions paracentesis is necessary in rare cases only. Chronic pericarditis of rheumatic origin is not the type requiring surgery in contrast to that due to tuberculosis.

**Prevention** The prevention of rheumatic fever and thereby of rheumatic heart disease has become a practical reality. It consists to date of several procedures: (1) improvement of living conditions; (2) protection against hemolytic streptococcus infection by contact with an infected individual; (3) the prophylactic use of penicillin in the case of a susceptible person when there is such contact or when such infection begins in the individual concerned; and (4) avoidance when possible of residence in climatic areas (high and cold in particular) where hemolytic streptococcus infection and rheumatic fever are common.

**Differential diagnosis** Rheumatic heart disease in active form has to be differentiated from any acute infection, especially if there happen to be heart murmurs. The differentiation is generally easy in older children and adults because of joint and heart signs and symptoms, but in very young children in whom the rheumatic infection is ill defined the problem may be a very difficult one to be solved only by continued and careful observation. In young adults with chronic rheumatic heart disease it may sometimes be difficult to distinguish at first whether a new infection is a recurrent rheumatic attack or subacute bacterial (*Streptococcus viridans*) endocarditis. The fewer joint symptoms, longer course, wider temperature swings, greater anemia and eventual appearance of characteristic signs of embolism, clubbed fingers, splenomegaly and positive blood culture gradually allow the differentiation of subacute bacterial endocarditis from acute rheumatism. The intradermal reaction to the toxic filtrate of the hemolytic streptococcus is generally positive in the rheumatic infection and generally negative in subacute bacterial endocarditis; this is helpful but not conclusive. It is important to note that the active rheumatic infection and subacute bacterial endocarditis may occur simultaneously in the same case (Kelson and White, 1945).

Septic chronic or rheumatoid arthritis offers as a rule little difficulty in the differential diagnosis, except when there happens to be a complication of heart disease or delayed A-V conduction, or when both diseases are present in the same case; then careful study is needed. Rare cases are however insoluble, there being no sharp boundary line, especially between rheumatoid arthritis and rheumatic fever.

Chronic rheumatic heart disease must be differentiated from conditions like severe anemia which give rise to functional cardiac dilatation and murmurs. This is generally easily done by the discovery of the underlying cause, such as anemia, and by the history which shows that the heart symptoms or signs appeared for the first time after the onset of the underlying disease.

The rheumatic type of heart disease must be differentiated from other types, not always an easy procedure. The age, the history of rheumatic infection, family incidence, the preponderant mitral valve involvement and the absence of other causative factors like syphilis, thyrotoxicosis, hypertension and cor

onary disease usually distinguish primary rheumatic heart disease from other types. It is to be remembered however that two or three different factors may simultaneously cause heart disease in a given case much care and good judgment must be exercised not only to determine these causes but also to decide their relative responsibility.

## BIBLIOGRAPHY

## RHEUMATIC HEART DISEASE

- Altschule M D "The Relation Between Prolonged P R Interval and Auricular Fibrillation in Patients with Rheumatic Heart Disease" *Am Heart J* 1939 XVIII 1
- Aschoff L. "Zur Myocarditis Frage" *Verhandl d deutsch path Gesellsch* 1904 VIII 46
- Baehr G and Schiffrin A "The Rarity of Glomerulo-nephritis in Rheumatic Fever and Its Significance" *Libman Anniversary Volumes* 1932 I 125
- Bland, E F., and Jones T D "Clinical Observations on the Events Preceding the Appearance of Rheumatic Fever" *J Clin Investigation* 1935 XIV 633
- Bland, E F Jones T D and White P D "Disappearance of the Physical Signs of Rheumatic Heart Disease" *JAMA* 1936 CVII 569
- Bland F F White P D and Jones T D "The Development of Mitral Stenosis in Young People with a Discussion of the Frequent Misinterpretation of a Middiastolic Murmur at the Cardiac Apex" *Am Heart J* 1935 X, 995
- Bouillaud, J. *Traite clinique du rhumatisme articulaire* J B Bailliere Paris 1840
- Brown M G and Wolff L. "Recovery from Acute Rheumatic Fever Without Permanent Cardiac Damage" *New England J Med* 1940 CCXXXIII 242
- Bruenn H G "The Mechanism of Impaired Auriculoventricular Conduction in Acute Rheumatic Fever" *Am Heart J* 1937 XIII 413
- Chang, F C and Dieuaide F R "Clinical Study of Rheumatic Fever in China" *Chinese M J* 1937 LI 381
- Chavez, I "The Incidence of Heart Disease in Mexico" *Am Heart J* 1942 XXIV 88
- Clawson B J "Rheumatic Heart Disease" *Am Heart J* 1940 XX 454
- Coburn A F "The Factor of Infection in the Rheumatic State" Williams and Wilkins Co Baltimore 1931
- "Relationship of the Rheumatic Process to the Development of Alterations in Tissues" *Am J Dis Child* 1933 XLV 933
- "Salicylate Therapy in Rheumatic Fever Rational Technic" *Bull Johns Hopkins Hosp* 1943 LXXIII 435
- Coburn A F and Moore L V "A Follow up Report on Rheumatic Subjects Treated with Sulfanilamide" *JAMA* 1941 CXVII 176
- Coombs C F *Rheumatic Heart Disease* with an Introduction by F J Poynton John Wright & Sons Ltd London 1924
- Decherd, G M Jr and Herrmann G R "Rheumatic Heart Disease in Texas" *Texas State J Med* 1943 XXXIX 229
- Fahr T "Beitrag zur Frage der rheumatischen Granulomatose (Polyarthritis rheumatica Rheumatismus infectiosus Graff)" *Klin Wchnschr* 1929 VIII 1995
- Faulkner J M and White P D "The Incidence of Rheumatic Fever Chorea and Rheumatic Heart Disease with Especial Reference to Their Occurrence in Families" *JAMA* 1924 LXXXIII 425
- Ferris E B Jr and Myers W K "Initial Attacks of Rheumatic Fever in Patients Over Sixty Years of Age" *Arch Int Med* 1935 LV 809
- Geiger J C Sampson J I Miller R C and Gray J P "A Survey of Heart Disease Morbidity in San Francisco" *Am Heart J* 1936 XII 137
- Gelfman R "The Incidence of Acute and Subacute Endocarditis in Rheumatic Heart Disease" *Ann Int Med* 1943 XIX 253
- Goldblatt H "Rheumatic Pancarditis with Functional and Anatomical Lesions of All Four Valves" *Libman Anniversary Volumes* 1932 II 507

- Graham H C Rheumaticositis *J Oklahoma M A* 1932 XXV 427
- Gross L and Fried B M Lesions in Auriculoventricular Conduction System Occurring in Rheumatic Fever *Am J Path* 1936 XII 31
- Gross L and Friedberg C K Lesions of Cardiac Valve Rings in Rheumatic Fever *Am J Path* 1936 XII 469
- Hansen A E Platou R V and Dwan P F Prolonged Use of Sulfonamide Compound in Prevention of Rheumatic Recrudescences in Children Evaluation Based on Four Year Study on Sixty four Children *Am J Dis Child* 1942 LXIV 963
- Harrison T R and Levine S A Notes on the Regional Distribution of Rheumatic Fever and Rheumatic Heart Disease in the United States *South M J* 194 XVII, 914
- Hedley O F Trends Geographical and Racial Distribution of Mortality from Heart Disease Among Persons 5-24 Years of Age in the United States During Recent Years (1922-1936) *U.S. Pub Health Rep* 1939 LIV 2271
- Hochrein M Über Angina Pectoris bei Mitralklappenstenose *Deutsch Arch f klin med* 1930 CLXIX 195
- Howard C P The Rheumatic Lung *Ann Int Med* 1933 VII 165
- Hubbard J P and Griffin W A Open Air Sanatorium Care for Patients with Rheumatic Fever and Rheumatic Heart Disease *New England J Med* 1940 CCXXIII 968
- Jones T D and Bland E F Clinical Significance of Chorea as a Manifestation of Rheumatic Fever A Study in Prognosis *JAMA* 1935 CV 571
- Rheumatic Fever and Heart Disease Completed Ten Year Observations on 1000 Patients *Tr A Am Physicians* 1942 LVII 267
- Jones T D White P D Roche C F Perdue J J and Ryan H A "The Transportation of Rheumatic Fever Patients to a Subtropical Climate" *JAMA* 1937 CVIII 1308
- Kaiser A D Results of Tonsillectomy A Comparative Study of Twenty two Hundred Tonsillectomized Children with an Equal Number of Controls Three and Ten Years after Operation *JAMA* 1930 LCV 837
- Kissane H W and Koons R A "Intra Uterine Rheumatic Heart Disease" *Arch Int Med* 1933 LII 905
- Kuttner A G and Reyersbach G "The Prevention of Streptococcal Upper Respiratory Infections and Rheumatic Recurrences in Rheumatic Children by the Prophylactic Use of Sulfanilamide" *J Clin Investigation* 1943 XXII 77
- Medical Research Council, England "Social Conditions and Acute Rheumatism Special Report Series No 114 Report of Committee on Child Life Investigations London 1927
- Mote J R and Jones T D Studies of Hemolytic Streptococcal Antibodies in Control Groups Rheumatic Fever and Rheumatoid Arthritis *J Immunol* 1941 VLI 35
- Paul J R "Pleural and Pulmonary Lesions in Rheumatic Fever" *Medicine* 1948 VII 383
- The Epidemiology of Rheumatic Fever and Some of Its Public Health Aspects* American Heart Association New York 2nd ed 1943
- Paul J R and Dixon G L "Climate and Rheumatic Heart Disease A Survey Among American Indian School Children in Northern and Southern Localities" *JAMA* 1937 CVIII 2096
- Perry C B "Rheumatic Heart Disease in Identical Twins" *Arch Dis Childhood* London 1940 XV 177
- Poynton F J and Paine A *Researches on Rheumatism I and A* Churchill London 1913
- Rabinowitz M A Rheumatic Pneumonia *JAMA* 1936 LXXXVII 142
- Reyersbach G and Kuttner A G "Studies on the Auriculoventricular Conduction Time of Normal Children and of Rheumatic Children Without Signs of Rheumatic Activity" *Am Heart J* 1940 XX 573
- Robey W H (Representing New England Heart Association) "A Cardiac Survey of Children in Boston Public Schools" *Nations Health* 1927 IX No 12 p 21
- Schwarz, H "An Unusual Case of Acute Rheumatic Fever in an Infant" *Lihman Anniversary Volumes* 1932 III 1061

- Seegal D and Seegal B C "Studies in the Epidemiology of Rheumatic Fever Annual Incidence in Some Hospitals in the United States Its Possessions and Canada" *JAMA* 1927 LXXXIX 11
- St Lawrence W "The Family Association of Cardiac Disease Acute Rheumatic Fever and Chorea A Study of One Hundred Families" *JAMA* 1922 LXXIX 2051
- Stone C T and Vanzant F R "Heart Disease as Seen in a Southern Clinic A Clinical and Pathological Survey" *JAMA* 1927 LXXXIX 1473
- Swift, H F "Rheumatic Heart Disease Pathogenesis and Etiology in Their Relation to Therapy and Prophylaxis" *Medicine* 1940 XIX 417
- Features Which Suggest Public Health Consideration of Rheumatic Fever *Bull New York Acad Med* 1940 XVI 501
- Thomas C B and France R (and Reichsman F) "Prophylactic Use of Sulfanilamide in Patients Susceptible to Rheumatic Fever" *Bull Johns Hopkins Hosp* 1939 LXIV 67 (and *JAMA* 1941 CXVI 551 and *Bull New York Acad Med* 1942 XVIII 508)
- von Glahn W C "Auricular Endocarditis of Rheumatic Origin" *Am J Path* 1926 II 1
- Walsh B J and Sprague H B "Character of Congestive Failure in Children with Active Rheumatic Fever" *Am J Dis Child* 1941 LXI 1003
- Wedd A M "Complete Heart Block in Acute Rheumatic Fever" *Am Heart J* 1937 XIV 719
- Wells W C "On Rheumatism of the Heart" *Tr Soc Improvement M and Chir Knowl* London 1810 CXI 372
- White P D "Acute Heart Block Occurring as the First Sign of Rheumatic Fever" *Am J M Sc* 1916 CLII 589
- White P D and Bland E F "Mitral Stenosis After Eighty" *JAMA* 1941 CXVI 7001
- White P D and Jones T D "Heart Disease and Disorders in New England" *Am Heart J* 1928 III 302
- Wilson M G "Rheumatic Fever The Commonwealth Fund New York 1940
- Wood J E Jr Jones T D and Kimbrough R D "The Etiology of Heart Disease Clinical Study of 623 Cases with Certain Observations on Race and Climate" *Am J M Sc* 1926 CLXXII 185

## Recent References (1944-1950)

- Appleman D H Feiman M S and Harris L "Acute Rheumatic Fever in the Aged" *Am Heart J* 1949 XXXVII 982
- Armstrong D B and Wheatley G M "Studies in Rheumatic Fever Metropolitan Life Ins Co New York 1944
- Ash R "Rheumatic Infection in Childhood Fifteen to Twenty Year Follow up Caution Against Early Ambulant Therapy" *Am J Dis Child* 1948 LXXVI 46
- Barber H S "Rheumatic Fever in R A F Results of Treatment at Convalescent Center" *Brit M J* 1946 II 83
- Barnes A R "Effects of Cortisone and ACTH in 14 Patients with Acute Rheumatic Fever" *Proc Staff Meet Mayo Clinic* 1950 XXV 478
- Barroso-Moguel R and Costero I "Evolución de las lesiones valvulares durante la fiebre reumática" *Arch del Inst de cardiol de Mexico* 1943 XIX 663
- Blackman N S and Hamilton C I Jr "Serial Electrocardiographic Changes in Young Adults with Acute Rheumatic Fever Report of 62 Cases" *Ann Int Med* 1948 XXIX 416
- Blanchard K C et al "The Effect of 3 Hydroxy 2 Phenylcinnamic Acid upon Rheumatic Fever" *Bull Johns Hopkins Hosp* 1950 LXXXVII 50
- Bos A K "Some Observations on the Past History and Clinical Studies in Rheumatic Heart Disease as Found in Bengal" *Indian Heart J* 1949 I 68
- Cannon J F "Incidence of Rheumatic Heart Disease in Rocky Mountain Region" *Rocky Mountain M J* 1946 XLIII 25
- Coburn A F and Young M C "The Epidemiology of Hemolytic Streptococcus" Williams & Wilkins Co Baltimore 1949
- Cortes C and Villarreal H "Revision de 1 160 Casos de Endocarditis Valvular Reu

- matica Aspectos clinicos" *Arch del Inst de Cardiol de Mexico* 1947 XVII 775  
and *Am Heart J* 1947 XXXIII 715
- Craige E Almurung M M Bland E F and Massell B F "The QT Interval in Rheumatic Fever" *Circulation* 1950 I 1338
- Crowley N "Hyaluronidase Production by Hemolytic Streptococci of Human Origin." *J Path & Bact* 1944 LVI 27
- Denny F W Wannamaker L W Brink W R Rammelkamp C II Jr and Custer E A "Prevention of Rheumatic Fever Treatment of the Preceding Streptococcal Infection" *JAMA* 1950 CXLIII 151
- Dodge K G Baldwin J S and Weber M W "Prophylactic Use of Sulfanilamide in Children with Inactive Rheumatic Fever" *J Pediatr* 1944 XXIV 483
- Edstrom G "Can Rheumatic Infection Be Influenced by Artificial Tropical Climate?" *Acta med Scandinav* 1944 CXVII 376
- Ergatan J A Forbes G B and Case D M "Salicylate Intoxication in Infant and Young Child Report of 13 Cases" *J Pediatr* 1947 XXX 129
- Fashena G J "The Incidence of Rheumatic Fever in Texas with Particular Reference to the Dallas Area" *Texas State J Med* 1944 XXXIX 474
- Fearby W R "Rheumatic Fever in the Canadian Army" *War Med* 1944 VI 139
- Filberbaum M B Griffith G C Solley R F and Leake W H "Electrocardiographic Abnormalities in 6 000 Cases of Rheumatic Fever" *California & West Med* 1946 LXIV 340
- Fischel E E and Pauls R H "Serologic Studies in Rheumatic Fever I Phase Reaction and Detection of Autoantibodies in the Rheumatic State" *J Exper Med* 1949 LXXXIX 669
- Foster F P McEachern G C Miller J H Ball F E Higley C S and Warren H A "The Treatment of Acute Rheumatic Fever with Penicillin" *JAMA* 1944 CXXVI 281
- Francisco R "Rheumatic Heart Disease in the Tropics with Special Reference to Its Incidence in Puerto Rico" *J B Lippincott Co Clinics* 1947, V 971
- Freud P Rook G D and Brunhofer A "Reactivation of Rheumatic Fever by Small pox Vaccination" *J Pediatr* 1950 XXXVI 635
- Gardner F E and White P D "Coronary Occlusion and Myocardial Infarction Associated with Chronic Rheumatic Heart Disease" *Ann Int Med* 1949 XXXI 1003
- Glendy R E "Rheumatic Diseases in Southwestern Virginia" *Virginia M Monthly* 1948 LXXV 334
- Goerner J R Massell B F and Jones T D "Use of Penicillin in the Treatment of Carriers of Beta Hemolytic Streptococci Among Patients with Rheumatic Fever" *New England J Med* 1947 CCXXXVII 576
- Griffith G C Moore F J McGinn S and Cosby R S "Familial Incidence of Rheumatic Fever II A Statistical Study of the Familial and Personal History of Rheumatic Fever" *Am Heart J* 1948 XXXV 444
- Hardgrove M Whittier L and Smith E R "Rheumatic Fever in Panama" *JAMA* 1946 CXXX 488
- Harris T N "Failure of Massive Salicylate Therapy to Suppress the Inflammatory Reaction in Rheumatic Fever" *Am J M Sc* 1947 CCXIII 482
- "Studies on the Relation of the Hemolytic Streptococcus to Rheumatic Fever I Review of Serologic Literature" *Am J Dis Child* 1948 LXXVI 411
- Harris T N Abrams W B Leo T F P and Hubbard J P "Cortisone Therapy in Acute Rheumatic Carditis Preliminary Observations" *Circulation* 1951 III 215
- Harris T N and Harris S "Studies in the Relation of the Hemolytic Streptococcus to Rheumatic Fever V Streptococcal and Anti hyaluronidase (mucin-clot prevention) Titers in the Sera of Patients with Rheumatic Fever Streptococcal Infection and Others" *Am J M Sc* 1949 CCXVII 174
- Hartz P H and Van der Sar A "Occurrence of Rheumatic Carditis in Native Population of Curaçao Netherlands West Indies" *Arch Path* 1946 XLI 32
- Hench P S Kendall E C Slocumb C II and Polley H F "Effects of Cortisone Acetate and Pituitary ACTH on Rheumatoid Arthritis Rheumatic Fever and Certain Other Conditions A Study in Clinical Physiology" *Arch Int Med* 1950 LXXV 545
- Hench P S Slocumb C H Barnes A R Smith H L Polley H F and Kendall

- E C "The Effects of the Adrenal Cortical Hormone 17 hydroxy 11-dehydrocorticosterone (Compound E) on the Acute Phase of Rheumatic Fever Preliminary Report *Proc Staff Meet Mayo Clinic* 1949 XXIV 77
- Holoubek J E., and Holoubek A H "Heart Disease in the South II A Statistical Survey of One Hundred Seventeen Deaths Due to Rheumatic Heart Disease *Am Heart J* 1947 XXXIV 709
- Jones, T D "The Diagnosis of Rheumatic Fever *JAMA* 1944 CXXVI 481
- Juch, A. and White P H "The Cause of Death in Rheumatic Heart Disease in Adults" *JAMA* 1944 CXXV 767
- Keith, J D., and Pequegnat L A "Some Observations on the Prevalence of Rheumatic Heart Disease in Canada" *Canad J Pub Health* 1947 XXXVIII 111
- Kelson, S H and White P D "Notes on 250 Cases of Subacute Bacterial (Streptococcal) Endocarditis Studied and Treated Between 1927 and 1939 *Ann Int Med* 1945 XXII 40
- Kohn K H Milzer A and MacLean H "Oral Penicillin Prophylaxis of Recurrences of Rheumatic Fever Interim Report on Method After a Three Year Study *JAMA* 1950 CXLII 20
- Kutner A G "Sulfonamide Prophylaxis for Prevention of Rheumatic Recurrences" *J Pediat* 1945 XXVI 216
- Levine H D "Rheumatic Heart Disease in New Guinea Including Cardiovascular Survey of 200 Native Papuans" *Ann Int Med* 1946 XXIV 826
- Logue R and Hurst J W "Suspected Age of Onset of Twenty-six Patients with Rheumatic Fever Who Are Five Years of Age or Under In press 1951
- Lutok M J and Kuzma J F "Rheumatic Pneumonitis A Clinical Study of 12 Necropsy Proved Cases of Rheumatic Pneumonitis *J Lab & Clin Med* 1950 XXXVI 958
- MacIlwaine Y "The Relationship Between Rheumatic Carditis and Subacute Bacterial Endocarditis" *J Path & Bact* 1947 LIX 557
- McKeown E F "Experimental Serum Carditis and Its Relationship to Rheumatic Fever *J Path & Bact* 1947 LIX 547
- McMillan R L and Jones C C "Rheumatic Heart Disease in Northwest North Carolina *North Carolina M J* 1950 II 105
- Malmer M M and Amsterdam S D "Oral Penicillin in Prophylaxis of Recurrent Rheumatic Fever" *J Pediat* 1947 XXXI 658
- Mauro V "Studio clinico statistico sulla evoluzione e prognosi della cardiopatia reumatica I Evoluzione in general e complicazioni" *Cuore e circola* 1949 XXXIII 26
- "Studio clinico-statistico sulla evoluzione e prognosi della cardiopatia reumatica III I vizi cardiaci di origine reumatica nei soggetti di età superiore a 45 anni *Cuore e circola* 1949 XXXIII 76
- Massell B F *Rheumatic Fever and Rheumatic Heart Disease* Year Book Publishers Chicago 1951 in press
- Massell B F Dow J W and Jones T D "Orally Administered Penicillin in Patients with Rheumatic Fever" *JAMA* 1948 CXXXVIII 1030
- Massell B F and Warren J E "Effect of Pituitary Adrenocorticotrophic Hormone (ACTH) on Rheumatic Fever and Rheumatic Carditis" *JAMA* 1950 CXLIV 1335
- Massell B J Warren J E Patterson P R and Lehman H J "Antirheumatic Activity of Ascorbic Acid in Large Doses Preliminary Observations on Seven Patients with Rheumatic Fever *New England J Med* 1950 CCXLII 614
- Massell B F Warren J E Sturges G P Hall B and Craig E "The Clinical Response of Rheumatic Fever and Acute Carditis to ACTH *New England J Med* 1950 CCXLII 641 and 692
- Meyer K "The Biological Significance of Hyaluronic Acid and Hyaluronidase" *Physiol Rev* 1947 XXVII 335
- Milzer A. Kohn K. H. and MacLean H "Oral Prophylaxis of Rheumatic Fever with Penicillin Resistant Hemolytic Streptococci" *JAMA* 1948 CXXXVI 536
- Murphy G E and Swift, H F "Induction of Cardiac Lesions Closely Resembling Those of Rheumatic Fever in Rabbits Following Repeated Skin Infections with Group A Streptococci *J Exper Med* 1949 LXXXIX 687
- "The Induction of Rheumatic like Cardiac Lesions in Rabbits by Repeated Focal



- Infections with Group A Streptococcus Comparison with the Cardiac Lesions of Serum Disease" *J Exper Med* 1950 XCI 485
- Neuberger K T Geever E F and Rutledge E A "Rheumatic Pneumonia" *Arch Path* 1944 XXXVII 1
- Perez de los Reyes R de la Torre H Labourdette Scull J M and Junco J A La cardiopatía reumática en el niño cubano" *Arch de med Infantil* 1944 XIII 3
- Pitt Evans J A Discussion on the Management of Rheumatic Fever and Its Early Complications Oral Penicillin in the Prophylaxis of Streptococcal Infection and Rheumatic Relapse" *Proc Roy Soc Med* 1950 XLIII 206
- Quinn H W Rheumatic Heart Disease and Crowding A Survey of Rural and Urban Connecticut School Children *Am J Pub Health* 1948 XXXVIII 1071
- Reid J Watson R D and Sproull D H "Mode of Action of Salicylate in Acute Rheumatic Fever" *Quart J Med* 1950 XIX 1
- Rich A R and Gregory J E "Further Experimental Cardiac Lesions of Rheumatic Type Produced by Anaphylactic Hypersensitivity" *Bull Johns Hopkins Hosp* 1944 LXXV 115
- Robles Gil J "Incidence and Clinical Features of Rheumatic Fever in Mexico City" *Am Heart J* 1947 XXXIII 713
- Rothbard S Group A Streptococcal Infections and Rheumatic Fever" *Mich an S M Soc J* 1949 XLVIII 1126
- Rutstein D D "Need for a Public Health Program in Rheumatic Fever and Rheumatic Heart Disease" *Am J Pub Health* 1946 XXXVI 461
- Sampson J J Hahman P T Halverson W L and Shearer M C "Incidence of Heart Disease and Rheumatic Fever in School Children in Three Climatically Different California Communities" *Am Heart J* 1945 XXIX 178
- Sprague H H and Carmichael D B Jr "Rheumatic Valvular Disease in the Aged" *Geriatrics* 1950 V 239
- Svartz N and Ernberg T The Prognosis in Different Kinds of Rheumatic Valvular Lesions" *Scand med* 1947 XXIII 757
- Wedum B G Darley W and Rhodes F H Prevalence of Rheumatic Heart Disease at High Altitudes" *Am J Dis Child* 1950 LXXIX 205
- Wegria R and Smull A "Salicylate Therapy in Acute Rheumatic Fever" *J Pediatr* 1945 XXVI 211
- Wheatley G M "Rheumatic Fever A Summary of Present Concepts" *Pediatrics* 1949 III 680
- White P D "The Relative Incidence of the Etiologic Types of Heart Disease in New England Compared to That of 25 Years Ago An Analysis of 3000 Cases" 1951 in press
- Wilson M G and Helper H N "Effect of Pituitary Adrenocorticotrophic Hormone (ACTH) in Acute Rheumatic Carditis" *JAMA* 1951 CXLV 133
- Wilson M G and Lubschez E "Longevity in Rheumatic Fever Based on Experiences in 1042 Children Observed Over a Period of Thirty Years" *JAMA* 1948 CXXXVIII 794
- Young W R and Viko L E "Rheumatic Fever in School Children in Utah" *Rocky Mountain M J* 1950 XLVII 46

---

## CHAPTER 15

---

### ACUTE AND SUBACUTE BACTERIAL (INFECTIVE) ENDOCARDITIS

Penicillin and other new specific therapeutic agents have already greatly reduced the seriousness of the diseases discussed in the present chapter and we may hope that eventually the reduction or even complete control of hemolytic streptococcus and other infections and of rheumatic and congenital heart disease may render it obsolete. Much of what was printed in earlier editions of this book is now merely of historical interest.

---

A discussion of acute and subacute bacterial (infective) endocarditis (malignant endocarditis) follows naturally after the last two chapters because bacterial endocarditis has been frequent in early adult life and has been in its subacute form an important complication of rheumatic and of congenital heart disease.

These two types of cardiac infection have been called acute bacterial endocarditis and subacute bacterial endocarditis respectively because of their clinical characteristics. This terminology is useful for general discussion and classification but not so satisfactory as is the terminology based on the specific causative bacteria, the names of which should always be employed in preference to the general term provided we know what the bacteria are. For example, *Staphylococcus aureus* or *pneumococcus* endocarditis is preferable to acute bacterial endocarditis as a diagnosis and *Streptococcus viridans* or *alpha hemolyticus* endocarditis is a better term than subacute bacterial endocarditis. The word *infective* is sometimes employed instead of *bacterial* and in former days both of these groups of infection of the heart were classed together as *malignant endocarditis*, a designation with much justification because of the almost invariably fatal outcome in those days but unsuitable because of the customary restriction of the word *malignant* to new growths and because of the high recovery rate nowadays.

In a large series of cases of acute and subacute bacterial endocarditis (199 cases with 138 autopsies) studied 25 years ago the responsible organisms were found as shown in Table 7 page 386.

Acute and subacute bacterial endocarditis are alike in that they are both serious diseases attended by invasion of the endocardium by virulent organisms almost wholly of the coccus family, there may be a similar invasion of the walls of the great arteries (bacterial endarteritis). The duration and virulence of the diseases are the only points in which they differ clinically. An arbitrary borderline of two months has been set between them. If the infection is a violent one lasting but a few days or weeks it has been called acute bacterial endocarditis; if it is slow in its course lasting over two or three months

Table 7

## BACTERIA CAUSING INFECTIVE BACTERIAL ENDOCARDITIS

	<i>Per Cent</i>
<i>Streptococcus</i>	57
<i>Pneumococcus</i>	14
<i>Staphylococcus aureus</i>	13
<i>Gonococcus</i>	11
<i>Influenza bacillus</i>	4
<i>Staphylococcus albus</i>	1 (Thayer 1925)

it has been called subacute bacterial endocarditis. Generally the latter is caused by one organism, the *Streptococcus viridans*, while the former is caused by any one of a large number of organisms. Rarely a *Streptococcus viridans* infection is so rapid that it falls into the acute bacterial group, and rarely one of the other organisms is so much resisted that it falls into the subacute bacterial group, as happens infrequently in the case of the gonococcus or of the influenza bacillus.

A high mortality was once characteristic of these diseases, prior to the use of penicillin early in 1944, but now recoveries are the rule and preventive measures are also highly effective, especially in the case of the acute type. Mild infection with these organisms resulting in demonstrable valvular deformity after recovery may possibly account for some of the chronic valvular disease found in cases without a history of a rheumatic infection, but the extent to which this occurs is not actually known and must be regarded still as an open question. In the present state of our knowledge it is reasonable to assume that the majority of cases of chronic nonsyphilitic valvular disease are rheumatic in origin.

Finally there is a considerable number of cases of very fresh endocarditis of slight or moderate degree discovered only by the pathologist at postmortem examination of individuals dying of a great variety of diseases. Such terminal endocarditis is of academic and pathologic interest alone for it usually can not be diagnosed clinically and has little or nothing to do with the death of the patient. We do not ordinarily designate under the term acute bacterial endocarditis this slight terminal endocarditis that has little or no clinical significance.

## ACUTE BACTERIAL ENDOCARDITIS

Acute bacterial endocarditis or endarteritis consists of an acute nonrheumatic invasion of endocardium or arterial endothelium either uncomplicated or as a part of other acute illness. It is attended by the symptoms and signs of a severe infection and in days gone by ended often in fact usually in death in the course of two months but now recovery is the rule in the rare cases that still appear. Cases in which it occurs number well under 1 per cent of all types of heart disease and of all types of endocarditis if we exclude the terminal endocarditis that has no clinical significance.

**Etiology Cause** The bacterium responsible for this disease may be any one of several organisms generally either the *Streptococcus hemolyticus*, the *Staphylococcus aureus*, the *Bacillus coli communis*, the *pneumococcus*, the *gonococcus* or the *meningococcus*. These six infecting organisms had been found in acute bacterial endocarditis in Boston before the days of penicillin in the following relative frequency making up nearly 100 per cent of the total of cases: the *Streptococcus hemolyticus* 43.6 per cent, the *Staphylococcus aureus* 22.8 per cent, the *Bacillus coli communis* 10.5 per cent, the *pneumococcus* 8.4 per cent, the *gonococcus* 4.2 per cent, and the *meningococcus* 4.2 per cent (Phipps 1932 with additional data by Dexter personal communication, a total of 48 autopsied cases of acute bacterial endocarditis).

Other bacteria that have been reported as rare causes of acute bacterial endocarditis are the *Staphylococcus albus*, the typhoid bacillus, the *enterococcus*, the *Micrococcus tetragenus*, the *Bacterium acidilactici*, the *Streptococcus viridans*, the parainfluenza bacillus (Russell and Fildes 1928, Fox 1935), the plague bacillus, *Brucella melitensis* (Malta or undulant fever bacterium) and the *Micrococcus endocarditidis rugatus*.

These organisms enter the circulation and attack the heart usually in the course of severe illness elsewhere in the body such as pneumonia, puerperal infection, gonorrheal rheumatism, abscesses, pyemia, tonsillitis and meningitis. In one series of 400 fatal cases of pneumonia examined post mortem 22 instances of pneumococcus vegetative endocarditis were found (Menetrier 1919) and in another series of 337 fatal cases of pneumonia there were 14 cases of pneumococcus endocarditis (4.15 per cent) (Lord 1932). In a series of 402 fatal cases of puerperal fever acute streptococcus endocarditis was found 8 times (Ruiz and Garcia 1926). Happily all this is now essentially past history since there is at present specific therapy for almost all these primary infections.

There is another source of infection that is not yet under adequate control and that is septicemia (especially with a staphylococcus) resulting from the self-medication hypodermically by narcotic addicts (Hussey et al 1944, Luttgens 1949). In such cases there is usually no pre-existing valvular disease.

**Age** Acute bacterial endocarditis may occur at any age from infancy to

old age but it is most frequent in the fifth decade. It may rarely occur also in fetal life.

**Sex.** Males are more subject to the disease than are females (73 per cent males to 27 per cent females in Phipps series 1932).

**Predisposing factors.** Although this acute cardiac infection may occur in hearts previously undamaged, it is more likely to attack those hearts already diseased with rheumatic lesions or congenital defects or arteriosclerotic changes where the soil is more suitable (60 per cent of Phipps series 1932).

**Pathology.** In acute bacterial endocarditis the valve cusps and frequently also the chordae tendineae and endocardium of atrium or ventricle (more commonly the left) and sometimes even the intima of aorta or patent ductus arteriosus are the site of the deposition of thrombi called vegetations. These vegetations are of varying size, sometimes as large as peas or beans, and they consist of irregular masses of fibrin, leukocytes, and colonies of bacteria. Any valve may be markedly involved, but the pulmonary is only rarely affected. In acute bacterial endocarditis, though less strikingly than in rheumatic heart disease, the valves of the left side of the heart are more frequently involved than those of the right side. The aortic valve is about as frequently affected as is the mitral. In a series of 23 cases of pneumococcus endocarditis, the left side of the heart was involved alone in 18, the right side alone in 3, and both sides in 2, while the mitral valve was affected in 13, the aortic valve in 12, both mitral and aortic valves in 5, and the tricuspid in 5, in one of which the pulmonary valve also was involved (Lord 1932). In a series of 58 cases of gonococcus endocarditis, the valve lesions were left-sided in 48, and the aortic valve was involved in 35 of these (Lion and Levy Bruhl 1922).

Ulceration of the endocardium of valve or heart wall or of the wall of the aorta or other arteries is common in the more severe cases; this is sometimes followed by perforation or aneurysms of cusps, rupture of chordae tendinae, abscesses of the valve rings, and even by small aneurysmal cavities in the aortic or other arterial wall (called mycotic aneurysms).

With recovery, scarring undoubtedly takes place, but whether or not such recovery is responsible for a few of the cases of chronic aortic or mitral stenosis, we have no certain knowledge.

Coincident myocardial or pericardial disease is uncommon. There may be found pyemic abscesses in the heart muscle or infarction due to coronary embolism arising from thrombi on the endocardium; septic pericarditis is also possible in such cases but is rare.

**Symptoms.** The symptoms of acute bacterial endocarditis are simply those of any very severe infection with septicemia: fever of septic type with wide swings as a rule, often with normal temperature in the morning and  $103^{\circ}$ ,  $104^{\circ}$  ( $40^{\circ}$  C) or  $105^{\circ}$  F in the evening; chills and sweating; prostration and delirium. In addition, if the disease continues as long as a few weeks, there tend to be symptoms from embolism caused by pieces of the endocardial thrombi blocking arteries to viscera, extremities, or brain, and pain and other localizing symptoms, such as hemoptysis from pulmonary infarction or hemiplegia from

cerebral embolism. The involvement of the heart itself rarely causes symptoms.

**Signs.** The patient appears very sick with little to point to the source of trouble except for embolic phenomena and the appearance of anemia and heart murmurs (or their increase) if the disease lasts long enough. Some times there are no definite signs, the fever being accounted for by other evidence of infection while the heart condition is discovered only at postmortem examination. There is usually a high (polymorphonuclear) leukocytosis of 20 000 to 30 000 or more unless the infection has completely overwhelmed the resistance of the patient. A secondary anemia develops rapidly but does not become so severe as in the subacute variety of bacterial endocarditis because of the short duration of the disease. There may be petechial hemorrhages into the skin and in rare cases even extensive purpura. There may be defective atrioventricular conduction shown by increase of the *P R* interval of the electrocardiogram beyond 0.2 second but this is rare. Arrhythmias are very uncommon. The most important method of study is that of blood culture. In the presence of this disease a positive blood culture is usually obtained at the second or third attempt if not at the first, the cause of the infection is thus discovered.

**Course and prognosis.** Acute bacterial endocarditis formerly progressed in rapid strides to a fatal termination in the course of days or weeks. Death was usually the result of toxemia but sometimes it came from embolism of brain, lung or coronary circulation. Very infrequently was it due to heart failure. The beginning of effective specific therapy by penicillin, the sulfonamides and other medication during the past decade has changed the picture completely so that now fatalities are uncommon and acute bacterial endocarditis is usually cured before it starts by the control of the underlying disease, whether pneumonia, meningitis, gonorrhea or other acute infection. Thus the diagnosis of acute bacterial endocarditis has now become not only very difficult but also very rare. It can still be suspected by the careful physician who notes the onset of the heart murmurs of valvular involvement during the course of pneumonia or sepsis and who observes the persistence of these murmurs and the development of cardiac enlargement on recovery.

**Complications.** Embolism, secondary anemia and heart failure have already been noted as important complications. Another occasional complication that may be serious or even fatal is the tendency to hemorrhages such as may occur in any fulminating infection—purpura of skin, sclerae and mucous membranes and bleeding from nose, mouth, lungs or gastrointestinal tract.

**Treatment.** In the second edition of this book fourteen years ago it was stated that there is no specific treatment for the disease except in the very rare case of meningococcus endocarditis when the administration intravenously of active antimeningococcus serum may effect a cure; that when the pneumococcus of type 1 or type 2 is responsible it would seem rational to inject antipneumococcus serum; that in most cases of acute bacterial endocarditis all kinds of drugs, vaccines and serums have been tried in vain; that

transfusions also have failed and that the rare recovery except when antimeningococcus serum may help is due apparently to the patient's own resistance which is to be supported by every measure at one's command chiefly by good nursing care, food, quiet and avoidance of the administration of drugs except to relieve discomfort. A great advance was noted in the third edition seven years ago consisting of the use of the sulfonamide drugs (sulfanilimide, sulfapyridine, sulfathiazole, and sulfadiazine) which by controlling the underlying infections from pneumococcus, gonococcus, streptococcus and staphylococcus prevented, in some cases at least, this serious in fact previously fatal complication of acute bacterial endocarditis and now today we can happily record another, perhaps final, spectacular advance since penicillin has appeared to help to wipe out this dread disease.

**Differential diagnosis.** The two chief difficulties in diagnosis come (1) from easy confusion with the subacute variety of bacterial endocarditis and (2) from confusion with severe infection of other nature especially with persistence or recurrence of the original disease from which the endocarditis comes. In the former case the virulence of the acute variety of bacterial endocarditis, its shorter course, the recent history of other illness and blood culture findings generally make differentiation clear. In the latter case the differentiation may be impossible only the development of embolic phenomena of severe anemia or of murmurs pathognomonic of valvular involvement (usually an aortic diastolic murmur) may point eventually to acute bacterial endocarditis. It is impossible to distinguish the rare case of recovery with chronic valvular disease from one of rheumatic origin unless the pulmonary valve has been affected or the case has been observed during its development in the course of some serious infection like pneumonia.

#### SUBACUTE BACTERIAL ENDOCARDITIS (ALSO CALLED SUBACUTE INFECTIVE ENDOCARDITIS, CHRONIC ULCERATIVE ENDOCARDITIS AND ENDOCARDITIS LENTA)

Subacute bacterial endocarditis as a clinical entity is much more common than is the acute variety of malignant endocarditis. It consists of the invasion of the heart—chiefly of the valves—by the *Streptococcus viridans*, rarely by the gonococcus or influenza bacillus, until recently it resulted fatally after a lingering illness. Its frequency and seriousness make it of great importance. In New England 20 years ago it occurred in 1 to 2 per cent of all cardiac patients (White and Jones, 1928), in 7 to 8 per cent of persons with congenital cardiovascular defects (Abbott) and in about 5 per cent of cases of rheumatic heart disease. Because of its seriousness, subacute bacterial endocarditis has a relatively high hospital incidence in comparison with rheumatism, for example, in the years 1928 to 1931 there were 177 cases of subacute bacterial endocarditis admitted to the larger Boston hospitals in contrast to 772 cases of rheumatic fever (Morrison, 1932). The advent of the sulfonamide derivatives ten years ago altered the situation for the outlook.

was no longer entirely hopeless as it had been a moderate number of cures were recorded but the disease was still nearly 95 per cent fatal. It was early in 1944 that with proof of the efficacy of penicillin (Loewe) the outlook suddenly brightened and now recovery is possible in at least 80 per cent of the cases. Despite this great change in fact because of it a clear recognition of the details of the disease has become all the more important since the earlier the diagnosis is made the sooner the curative treatment can be started and the less will be the added damage to the heart and the risk from the common and serious complications such as embolism.

**Etiology Cause** The organism responsible for subacute bacterial endocarditis is in 90 to 95 per cent of the cases the *Streptococcus viridans* (Schott muller 1910) and in the other 5 to 10 per cent the gonococcus influenza or parainfluenza bacillus enterococcus or *Brucella abortus*. The typhoid bacillus has also been reported to give rise to a long-drawn-out endocarditis. There may be a mixed infection as by gonococcus and streptococcus (Orgain and Poston 1942 Olinger 1943) or there may be more than one strain of viridans streptococci in the same case (MacLean and Howell 1947). All these other organisms especially the gonococcus can cause a short virulent acute bacterial endocarditis but the *Streptococcus viridans* rarely does so.

**Predisposing factors** The chief predisposing factor is chronic heart disease particularly old rheumatic valvular disease (in about 80 per cent of the cases) and congenital cardiovascular defects (in about 10 per cent of the cases) especially in those with either bicuspid aortic valves (9 of 32 cases of Abbott's series and 11 of 52 of Gelfman and Levine's series) or ventricular septal defects (13 of 50 cases and 13 of 31 cases respectively) or patency of the ductus arteriosus (21 of 92 cases and 4 of 14 cases) or coarctation of the aorta (7 of 70 cases and one of 10 cases) in contrast to atrial septal defects (2 of 68 cases and none of 45 cases respectively). Abbott and Gelfman and Levine (1942) but a previously undamaged heart may infrequently also be the site of this disease. Rarely aortic valves damaged by syphilis may be involved in subacute bacterial endocarditis but in such cases there may be a coincident rheumatic valve lesion.

Focal infection as in diseased teeth tonsils and gums can be a predisposing factor (Weiss 1934) dental extractions are more commonly followed by subacute bacterial endocarditis than are any other recognizable events. There is a clear reason for this as indicated by the findings of Okell and Elliott (1935) in 40 instances after multiple tooth extractions in the presence of extensive disease of the gums positive blood cultures were obtained in 30 (75 per cent) in 60 instances after multiple tooth extractions in the presence of a moderate degree of gum disease there were positive blood cultures in 42 (70 per cent) and in 38 instances of the extraction of one or more teeth without detectable gum disease there were 12 positive blood cultures (34 per cent). The more often one inquires specifically about dental work or infection prior to the onset of subacute bacterial endocarditis the more often one finds it (up to about one third of the cases).



The mechanism of the endocardial involvement in subacute bacterial endocarditis has been variously considered. Direct blood stream infection of the endocardium damaged of old with small thrombi or ulcerations as footholds for the streptococci that happen to be circulating in the blood is probably the usual mode of involvement rather than the introduction of these organisms to the endocardium through blood vessels in the valves but it is possible that both methods of infection exist. Although the *Streptococcus viridans* is an occasional invader of the blood stream even in normal persons it causes no disease unless it enters in large numbers (as through foci of infection) or unless conditions favor its lodgment and growth as in individuals with chronic heart disease.

**Age** The age at which subacute bacterial endocarditis occurs varies from early childhood to old age. It is commonest between the ages of fifteen and thirty years. Of 250 cases in Kelson and White's series (1945) 6 were under ten years, 42 between ten and twenty, 79 between twenty and thirty, 53 between thirty and forty, 39 between forty and fifty, 21 between fifty and sixty, and 10 over sixty. The youngest cases on record are one and one half years old (Goetsch 1938), two and one half (complicating congenital heart disease) and five years old but the disease is very rare in young children. The oldest cases were eighty two years of age, a man who had apparently sclerotic valvular changes as a background of his infection (Willius 1940) and eighty seven years (Zeman 1945). *Streptococcus viridans* bacteriemia without endocarditis has been reported in two infants shortly after birth, the mothers being ill with subacute bacterial endocarditis themselves (Walser 1928). A collection from the literature has been made (Rost and Fischer 1928) of 64 cases under the age of fourteen years.

**Sex** Subacute bacterial endocarditis occurs somewhat more often in males than in females. In Kelson and White's series (1945) it was found in 161 males and 89 females and in a series of 328 cases collected by Blumer from the literature the ratio was 60 per cent males to 40 per cent females (Blumer 1923).

**Other factors** Other factors such as race, climate and social and economic status are relatively unimportant compared to that of the presence of chronic heart disease mentioned above except as they favor the predisposing cause, namely, rheumatic involvement. However it is possible, though not yet proved, that any illness, accident or exposure to cold and wet or to strain may help to precipitate the disease by favoring the bacterial invasion.

**Pathology** The pathologic picture in subacute bacterial endocarditis is primarily that of involvement of the endocardium of valves by the deposition of irregular masses of fibrin, leukocytes, erythrocytes and platelets enclosing bacteria and products of bacterial degeneration, called vegetations (Figures 87 and 88 see opposite page). These vegetations are larger than the thrombi in rheumatic endocarditis but they may not be so large as those of acute bacterial endocarditis. The chordae tendinae and left atrium and left ventricular endocardium are frequently involved by a spreading of the infection from the valve.

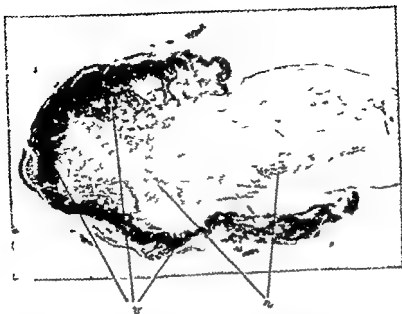


FIG 87 Microphotograph showing low power magnification of the cross section of the end of a cusp of the mitral valve infected by the *Streptococcus viridans* in subacute bacterial endocarditis. Note vegetation (v) encircling the cusp end and consisting mostly of masses of bacteria and fibrin (stained black). Also note inflammatory leukocytic reaction (r) in the cusp itself.



FIG 88 Photograph showing subacute bacterial (infective) endocarditis with vegetations on mitral valve and endocardium of left atrium. (Kindness of Dr Ronald Grant, Guy's Hospital London.)

cusps or by contact with the cusps that is, where the heart wall touches these vegetations on the cusp during the heart cycle. The intima of the aorta may also be infected either where aortic valve vegetations are in contact with it or elsewhere. An arteriovenous aneurysm may become infected by the *Streptococcus viridans*. Finally congenital defects: such as patent ductus arteriosus, coarctation of aorta and especially interventricular septal defects and bicuspid aortic valves may be the site of invasion by the *Streptococcus viridans*.

There may result from this inflammation of the endocardium an extension of the process into underlying tissues with deep ulceration or perforation or aneurysm formation in the valve cusps or local ulceration and aneurysm of the aorta (even with rupture). This type of aortic aneurysm like that resulting from acute bacterial endocarditis, is called a *mycotic aneurysm*. In very rare cases the process may cause an aneurysm in or a perforation through the ventricular septum or from left ventricle into right atrium or even a rupture of atrial wall. Also rarely invasion of the upper ventricular septal region may damage the atrioventricular bundle (of His) to cause heart block. The vegetations sometimes grow very large or elongated and if this occurs on the aortic valve the vegetations may partially block the mouths of the coronary arteries.

The valves of the left side of the heart are much more frequently involved than are those of the right side and the mitral valve oftener than the aortic though the great preponderance of mitral over aortic valve involvement seen in rheumatic heart disease does not hold here. Pulmonary valve involvement is rare in subacute bacterial endocarditis in contrast to its involvement in acute bacterial endocarditis. In a series of 90 autopsied cases of subacute bacterial endocarditis in which there was a specification of the valves that were involved in the process the mitral valve alone was affected in 25, the aortic valve alone in 18, both mitral and aortic in 38, mitral, aortic and tricuspid in 2, all four valves in 1, pulmonary and aortic in 2, tricuspid and ventricular septal defect in 1, pulmonary and ductus arteriosus in 1, pulmonary, aortic and ductus arteriosus in 1, and only the mural endocardium in the remaining 1 (Morrison 1932).

As already noted in the majority of cases *Streptococcus viridans* endocarditis is superimposed on chronic rheumatic valvular disease. It is probable that in communities where rheumatic heart disease is infrequent the predisposing factor of congenital defects is as important as is that of rheumatic valvular disease and in such communities one would expect to find the total incidence of subacute bacterial endocarditis considerably reduced in comparison with that in rheumatic areas. Out of 203 cases of subacute bacterial endocarditis analyzed in Boston 134 had clearly and others probably a rheumatic background, 11 had congenital defects, 3 an underlying syphilitic process and one a definite atherosclerotic basis (Morrison 1932). Markedly stenosed valves are less frequently attacked by subacute bacterial endocarditis; the less slightly deformed valves in chronic rheumatic heart disease are the ones found at autopsy to be more often the site of this fatal complication and they are the ones which during life give rise to the murmurs of valvular recur-

gitation (the systolic murmur of mitral origin at the apex and the diastolic murmur of aortic origin at the base)

Pericarditis in subacute bacterial endocarditis is rare but myocardial lesions have been reported (Bracht and Wachter 1909 Saphir 1946) consisting of diffuse inflammatory changes and of areas of infiltration in the interstitial tissue of the myocardium. These areas however are also found in other cardiac infections and include the Aschoff body which may or may not indicate the presence of a coincident rheumatic heart infection in some cases. Saphir has also described foreign body granulomas caused by calcific emboli arising from healed vegetations on the aortic valve in patients recently treated with penicillin or the sulfonamides.

After recovery from subacute bacterial endocarditis the extent of chronic valvular disease may be increased. Since however most of the valvular deformity is usually the result of previous rheumatic infection careful observation of the state of the heart before or at the onset of the subacute bacterial endocarditis is essential before it can be said that this disease caused or increased the valve deformity in a given case.

**Symptoms** The symptoms of subacute bacterial endocarditis are like those of any infection but are less severe than in acute bacterial endocarditis. Fever of varying grades occurs sometimes almost none at all and sometimes with wide daily swings of septic type as for example normal or subnormal temperature in the mornings and high fever (to 104° F or 40° C) in the evening. Fever may however be absent for days at a time and then recur at intervals. Chills and sweats are common. Anorexia, malaise, prostration and loss of weight and strength are usual although for days or even weeks at the onset there may be merely a feeling of fatigue with little fever. When embolism begins coming from thrombi in the heart local pain and other symptoms appear depending on the organ or the part of the body affected. Splenic, renal and cerebral infarctions are common. With increasing anemia there may be hemorrhages into skin and from nose, lungs and stomach—in addition to the embolic phenomena. Finally if the disease is not brought under control the toxic state increases and weakness and mental confusion may become marked before death ensues or myocardial failure may develop with dyspnea or hepatic congestive pain or both if the infection is exhausting whether or not it is itself cured. However with successful penicillin therapy at a relatively early stage of the disease nowadays, alert medical attention can in the majority of cases stop the process before any important complications take place.

**Signs** The characteristic signs of the disease are fever, a pallor due largely to secondary anemia and sometimes referred to as *café au lait* (Libman), petechial hemorrhages into the skin, mucous membranes and conjunctivae, splenomegaly, clubbing of the fingers and evidence of valvular or congenital heart disease. Rarely are all these signs pronounced in any given case usually the diagnosis must rest on two or three only generally supported however by a finding of the *Streptococcus viridans* by blood culture.

The superficial petechial hemorrhages may be found anywhere on the body

and should be searched for carefully, they may be limited to the conjunctivae to the chest or elsewhere. They are most commonly found on the forearms and hands, when located under the nails they are linear in shape and have been designated 'splinter hemorrhages'. They come and go often in crops in a given area, each spot rarely lasts more than a few days beginning as a small reddish or purplish dot under the skin not disappearing on pressure but gradually fading away within a week. The spots vary in size usually from that of a pin point to that of the head of a large pin. They may be produced in the forearm from the compression of the upper arm by a blood pressure cuff. Thus they are evidently the result of damage to vessel walls by a toxin which allows leakage of blood whenever pressure trauma or some other factor favors it. The petechiae are therefore related rather to a hemorrhagic tendency of which a common sign is nosebleed than to embolism. Petechial hemorrhages although very common in subacute bacterial endocarditis are not pathognomonic of the disease they are also found not uncommonly in acute rheumatism.

There is another sign of vascular origin often of value but not found in all cases of subacute bacterial endocarditis tender fingers and toes. This is due most commonly to embolism of or hemorrhage from a small vessel in a finger tip or in a toe and consists of a deep painful purplish slightly swollen indurated area the size of a pea or smaller in the pulp of the end of the finger. This lesion comes suddenly and disappears gradually in the course of a few days. It may be isolated or there may be several such lesions at the same time or in succession. Either fingers or toes may present this sign but more commonly the fingers are affected.

The so-called Osler's node (Osler 1909) as described first by Mullen of Hamilton and later by Osler himself is a much rarer phenomenon it consists of a raised red nodule (never hemorrhagic) in the skin of finger or toe and not beneath it  $\frac{1}{2}$  to  $1\frac{1}{2}$  cm in diameter with a whitish point in the center and lasting a day or two.

Still another sign and much the most important of those found in the fingers or toes of patients with subacute bacterial endocarditis is clubbing. This condition also found in congenital heart disease and certain pulmonary diseases is shown in Figure 63 page 298. In subacute bacterial endocarditis it is very variable in occurrence and degree. Clubbing is present in some measure in three quarters of all the cases but is well marked in only one half or somewhat less being most evident in the cases with enlarged spleens. It does not appear at the onset of the disease but only when it is well advanced after the first few weeks. Why it should occur in this disease has not been discovered but it is likely that local disturbance of the circulation (instead of general anoxemia with cyanosis as in congenital heart disease) causes capillary dilatation and increased soft tissue growth. Instead of cyanosis there is usually increased redness of the bulbous finger tips. When present clubbing is an important sign and should always be heeded but care must be taken not to confuse it with congenital or occupational abnormality of shape of the fingers. Although the

toes may be clubbed as well as the fingers their clubbing is generally less obvious Clubbing recedes with recovery and disappears completely

*Splenomegaly* is common in subacute bacterial endocarditis and its presence is a very helpful sign However in about a third of the cases the spleen cannot be felt on physical examination Its enlargement when evident is usually not great, a firm nontender edge being felt just below the left costal border On rare occasions it may become large enough to extend almost to the umbilicus Like clubbing of the fingers splenomegaly usually clears up with recovery

The presence of evidence of *chronic valvular disease* or of *congenital defects* is usual and is somewhat corroborative One finds commonly an apical systolic murmur of mitral regurgitation occasionally the early diastolic murmur of aortic regurgitation and less commonly the murmurs of mitral stenosis aortic stenosis or congenital defects Sometimes an important murmur develops in the heart under observation indicating the onset or the increase of valvular deformity during this infection There is usually slight cardiac enlargement The heart may however appear normal on physical examination during most and rarely during all of the illness one may be misled thereby In such cases there may be endocarditis of a congenitally bicuspid aortic valve without enough actual valvular deformity to produce significant murmurs

Arrhythmia due to atrial fibrillation complicating subacute bacterial endocarditis was formerly thought to be extremely rare in recent years it has been found that their coexistence occasionally though still uncommonly takes place for example McDonald (1946) has reported 36 cases of atrial fibrillation (12.6 per cent) among 286 patients with subacute bacterial endocarditis Of these 36 cases 24 were carefully analyzed 3 showed paroxysmal arrhythmia and 21 permanent Of the 21 5 had the infection first, 6 had the arrhythmia first and 10 had both when first seen Premature beats are occasionally found but are of little importance The rare occurrence of delayed atrioventricular conduction (heart block) suggests extensive involvement of the interventricular septum Pericarditis is extremely rare in subacute bacterial endocarditis

Blood pressure roentgenologic and electrocardiographic studies show little or nothing abnormal except for evidence of underlying valvular disease congenital defect or heart block which may or may not be due to the subacute bacterial endocarditis

*Blood studies* are of much importance *Secondary anemia* is common if the disease lasts six weeks or more with red cell count between 3 and 3.1 millions and hemoglobin at about 60 per cent somewhat lower figures of 2 to 3 millions of red cells and 40 to 50 per cent hemoglobin are also found but less frequently In rare cases the red count may drop to one million or less with hemoglobin of about 30 per cent A polymorphonuclear leukocytosis of slight to moderate degree (12 000 to 16 000) is common when there are complications such as embolism to spleen or elsewhere infrequently it is higher but more commonly it is lower often being recorded at a normal figure The blood smear shows achromia of red cells but only rarely polychromatophilia or change in size or shape of the cells The platelets are normal In a certain

small percentage of cases, perhaps 10 or 15 per cent, there are found in the blood smear occasional large endothelial phagocytic cells which are also found sometimes in other diseases their presence is somewhat helpful in corroborating the diagnosis The sedimentation rate is usually accelerated

*Blood cultures* carefully taken and repeated once or twice if necessary should be positive for the *Streptococcus viridans* in about 90 per cent of the cases A suitable culture medium is hormone broth with hydrogen ion concentration of pH 7.6 It is of interest to prepare pour plates in order to get some idea of the quantity of organisms by the number of colonies per plate which may vary from one to many Blood is collected in citrate flasks ( $\frac{1}{2}$  cc of 4 per cent sodium citrate in a 50 cc Pyrex flask) from which 2 cc and two 1 cc samples are pipetted into tubes of melted nutrient agar which is cooled to 45° C after the tubes are rolled a few times the mixtures are poured into Petri dishes and the colonies are read after two and four days (kindness of Dr. Louis Dienes) Cultures of venous blood usually suffice but on rare occasions cultures of bone marrow are positive when blood cultures are negative Arterial blood cultures are least satisfactory (Salazar Mallen, et al., 1947)

Titration of immune bodies in the blood in patients with subacute bacterial endocarditis has shown a high degree of such bodies much greater as a rule than in the blood of the normal control This test may perhaps prove helpful in establishing the diagnosis

The Wassermann reaction has sometimes been found positive in subacute bacterial endocarditis in the absence of syphilis this possibility should be remembered

The urine is not remarkable except for the frequent and important finding of numerous red blood corpuscles in the sediment There usually is not enough blood to appear macroscopically This finding in the sediment has been ascribed to renal infarction by multiple small emboli At postmortem examination glomerular lesions are frequently found (Baehr 1912) However it is probable that much of the blood in the urine is the result of minute hemorrhages comparable to those in the skin (petechiae) Albuminuria is commonly present if there is much fever or bleeding

*Course and prognosis* The gradual insidious onset of this disease often prevents any exact determination of the time of its beginning There may be a feeling of increasing fatigue and loss of appetite and sometimes there are vague joint and muscle pains the victim may appear pale listless and run down for a few weeks before fever or other symptoms force him to bed or to ask for medical advice Months sometimes elapse with no definite idea of what is wrong Usually however in the early weeks of the illness the temperature reaction anemia enlarged spleen or clubbing of the fingers and heart signs and blood culture show the presence of this serious illness Prior to 1944 the symptoms and signs would steadily increase with development of embolic phenomena and death often the result of complications commonly ensued a few months to a year or more after the onset of the disease the average duration of the illness being about six months

Recovery prior to 1939 occurred in less than 1 per cent of all cases of subacute bacterial endocarditis rose to 5 or 6 per cent when the sulfonamides were introduced in maximal and very disagreeable dosage and five years later in 1944 abruptly increased to a little over 50 per cent with the advent of moderate but still inadequate amounts of penicillin. Slowly in the five years that have elapsed since then when penicillin became available in larger and larger amounts and with increasing realization of the need of massive doses early in the disease and with the help of allies such as streptomycin at least 80 per cent of the patients have become curable. It is likely that the ultimate figure will approach 90 but it is also probable that there will always be fatalities due to four causes: (1) heart failure resulting from the extent of the heart disease itself plus the added strain of the infection and its treatment; (2) embolism to brain or elsewhere; and (3) intercurrent acute rheumatism; these three causes operating even in cured patients and finally (4) resistance in a few cases to all specific therapy.

It is to be remembered that a finding of the *Streptococcus viridans* in the blood by culture does not alone establish the diagnosis of subacute bacterial endocarditis even if chronic valvular disease (or a congenital cardiovascular defect) or fever is also present; the presence of all three of these findings is however almost conclusive in a given case. Positive blood cultures have been found without fresh endocarditis indicating that there is an illness of other nature present and not malignant endocarditis. A preponderant group of signs should be present to establish the diagnosis of subacute bacterial endocarditis. The clinical course is the most important clue. For full reliance on blood cultures several (at least 3 or 4) should be found positive.

There has been a very interesting small group of cases of subacute bacterial endocarditis mostly of historic interest now that became bacteria free but nevertheless went on for the most part to a fatal termination from uremia or heart failure; they were characterized by the subsidence of fever, negative blood cultures, anemia, brownish color of face and particularly severe glomerulonephritis (Libman 1913).

Finally advanced subacute bacterial endocarditis may be wholly or in large part symptomless prior to the occurrence of serious embolism which in the case of a woman 31 years old led rapidly to death from coronary occlusion (West 1931).

**Complications.** The chief complications of this disease are due to infarction of various organs from emboli that arise from the intracardiac (chiefly valvular) thrombosis. If these emboli are large and affect vital tissue a speedy death may follow. The most important infarctions are those of the heart itself by coronary embolism of brain and of kidneys. Cardiac infarction is very rare; hemiplegia or paralysis of lesser extent is not uncommon after cerebral embolism and hematuria may result from renal infarction or simply from leaking blood vessels. Hemorrhage of any serious moment is not often seen in this disease; rarely it may complicate cerebral embolism and result fatally. The renal damage may infrequently lead to uremia and death in a case of subacute



bacterial endocarditis. A large embolus may obstruct an important artery to an extremity like the femoral popliteal tibial brachial or digital artery but rarely causes gangrene with need of amputation. The spleen is one of the most common sites of infarction; this explains the very frequent severe pain in the region of the spleen in patients with subacute bacterial endocarditis. Mesenteric infarction may occur and it has been suggested that some pulmonary signs may be due to embolism of bronchial arteries. Pulmonary infarction is not common inasmuch as the endocardial vegetations are generally or preponderantly on the left side of the heart but with thrombi in the right heart chambers this too can occur. A long course of febrile illness in a patient with congenital heart disease affecting the right heart chambers complicated by pulmonary infarcts strongly suggests subacute bacterial endocarditis; in such cases blood cultures may fail to show the *Streptococcus viridans* until late in the disease and clubbing of the fingers and splenomegaly may be wanting (Blumgart 1933).

Heart failure of congestive type is sometimes but not often the cause of death; it is frequently present in slight or moderate degree brought on by the strain of infection and anemia in a heart already damaged; rarely is there enough additional damage to the heart from this infection to cause failure directly. Angina pectoris may rarely occur due to blocking of the mouths of the coronary arteries by the vegetations on the aortic valve, or to the added effects of aortic regurgitation and anemia. Atrial fibrillation occurs infrequently and heart block appears in rare cases.

Active rheumatism in the form of rheumatic fever or even of pancarditis may complicate subacute bacterial endocarditis; apparently excited by it in some cases and pre-existing in others; it was thought to be a complication in at least 17 and perhaps 4 more of Kelson and White's series of 250 cases (1945).

The secondary anemia itself if not well controlled by transfusion may become a grave complication favoring a fatal outcome. In his weakened condition the patient may fall a victim to a complicating infection like pneumonia.

Finally it is of some interest to note that pregnancy, childbirth and the puerperium may progress without any material difficulty despite subacute bacterial endocarditis (Mengert 1933) although there may be *Streptococcus viridans* bacteriemia in the infant (Walser 1928).

**Treatment.** In the first three editions of this book many different medicines and other empiric therapeutic measures were discussed but the only treatment that gave any promise at all was that with the sulfonamides especially sulfadiazine which was the least toxic while effecting rare cures. When the sulfonamides were forced beyond the point of endurable toxic results there was a slightly higher percentage of recoveries. Doses of 2 gm of a sulfonamide followed in two hours by another 2 gm initially and then 1 gm every four hours until the blood level reached close to 10 mg per 100 cc followed by adjustment of the dose to maintain that level in the course of a fortnight or two resulted

in a few cures. Such supplementary therapy may still be of value when penicillin and streptomycin are alone or in combination ineffective. Heparin and Dicumarol were added to this sulfonamide therapy in the early days with the thought that they might prevent the deposition of new thrombi on the endocardium while those already present were being sterilized, but practical experience during recent years has indicated that such addition to the treatment has not resulted in any gain and instead has been troublesome, expensive and even on occasion harmful.

It is of historic interest merely to insert herewith, without further comment except to note their failure, the imposing list of drugs and other therapy tried years ago in the vain effort to cure this dread disease: arsenic in various forms, mercury, gentian violet, salicylates, antiseptics of all kinds, vaccines, serums, transfusions including those from immunized donors, production of sterile abscesses, splenectomy, electrotherapy, diathermy, and hyperthermia. A few of these measures have had on occasion a somewhat helpful though not curative effect; transfusions have so acted when there has been a severe anemia and both splenectomy and hyperthermia have had their advocates.

Happily today one can be brief and explicit about therapy that is effective in the great majority of cases, as the result of the discovery reported by Fleming in 1929 that *Penicillium notatum*, a common mold, contained a potent antibacterial substance, of its purification and application by Florey and his colleagues in 1940, and of its curative effect in subacute bacterial endocarditis by Loewe in 1944. After the diagnosis has been established as early in the disease as possible, or if not proved, at least considered probable, after careful study, penicillin should be administered at once in adequate dosage and continued as a rule for six weeks, with a range of four to eight, or as much longer as may be deemed necessary in any particular case. A dose of 500,000 to 1,000,000 units a day should be given parenterally, if for any reason oral medication is given the daily dose must be 5 to 10 times greater to produce the same beneficial effect. If after a week or ten days there is no obvious effect of the 500,000 to 1,000,000 unit dose on fever, clinical course, or blood culture, the daily amount should be multiplied five times. Even as much as 20,000,000 units a day for weeks has been necessary to effect a cure in rare cases.

Common mistakes, quite natural in the early days of such therapy because of the limited supply of the penicillin, were to give too little at the start and to increase the size of the dose too slowly and too cautiously. It is far wiser to give a larger amount than may be necessary at the beginning rather than to allow the infection to continue too long with the hazard of serious complications. It is, however, best of all routinely to adopt the procedure of *in vitro* testing of the sensitivity to penicillin of the causative organism, whether *Streptococcus viridans* or not, since there has been shown to be a very definite relationship between this sensitivity and the curative dosage (Hunter, 1946; Clark et al., 1948). The great majority of the strains of the *Streptococcus viridans* are inhibited by 0.1 unit of penicillin per cubic centimeter of culture.

medium and so do not need maximal dosage but a few require 2 to 0.5 units and a very few up to 1 unit or more. It has been helpfully advised that for the first that is the more sensitive group a daily dose of 500 000 units be given for the second that is the intermediate group a dose of 1 to 2 million units, and for the third the most resistant group a dose of 5 to 20 million units a day. If these maximal doses are still ineffective adjuvant treatment with caronamide or streptomycin is in order (see below).

Various methods of administration of the penicillin have been introduced and they all have had their advocates as may be found on consulting the Bibliography of this chapter. Intramuscular injections in sterile saline or aqueous solution every two to four hours (usually three) day and night were in use most frequently and proved to be quite practical and effective. Constant intramuscular and intravenous drips were also curative earlier and had the advantage of producing a more constant blood level but the disadvantage of inconvenience. Penicillin in oil and beeswax proved helpful in establishing a fairly uniform absorption and blood concentration although without high levels (Hewitt 1947 Hoffman et al 1947) this procedure was especially convenient because it reduced the number of injections needed intramuscularly to two in twenty four hours and was recommended in particular for prophylaxis as in the case of dental extractions. Recently there has come into more or less routine use a preparation of penicillin with procaine (which has a beneficial twofold effect of rendering the injection painless and slow in absorption) which can be very conveniently and effectively injected intramuscularly in the dosage of 300 000 or 600 000 units every six hours giving satisfactory total daily doses of 1 200 000 or 2 400 000 units respectively.

Another important means of maintaining a more or less uniform and especially a higher (threefold or more) concentration of penicillin in the blood particularly useful in obstinate cases not responding well to lower concentrations is by adding caronamide or benemid which blocks the ordinarily rapid excretion of penicillin through the renal tubules (Beyer 1947 Boger et al 1947 1949 and 1950 Loewe et al 1947 Meads et al 1948 Burnell and Kirby 1951). Four grams of caronamide are given orally every three to four hours or  $\frac{1}{2}$  gm of benemid every six hours for days to weeks in order to produce a blood serum concentration of approximately 30 mg per 100 cc which is necessary in order to maintain a threefold or more increase of penicillin level. The drug must be used with some caution however in patients who have any suspicion of reduced kidney function beforehand and probably not at all when serious kidney disease is present. Also toxic symptoms such as nausea and vomiting may be induced in some cases. However the use of caronamide and benemid has resulted in cures by penicillin in cases not responding well without it.

Finally in cases fortunately very few in number in which penicillin is ineffective it may be necessary to resort to streptomycin alone or in addition or even to add sulfidiazine. This applies to organisms particularly gram negative bacilli and certain gram positive cocci which are very insensitive to

penicillin In such cases after the in vitro and brief in vivo testing with penicillin and in vitro testing with streptomycin the latter should be injected intramuscularly in the dosage of 0.5 to 1.0 gm (preferably the larger dose) every six hours for days depending on the clinical progress and toxic symptoms This gives a blood concentration of streptomycin of some 10 to 20 units (or micrograms) per 100 cc which is as a rule far greater than the in vitro sensitivity of the organism causing the disease There are two difficulties which render streptomycin much less satisfactory to deal with than penicillin (1) the toxic effects which include especially vertigo which may be permanent secondary to labyrinthitis fever dermatitis and pruritis and (2) increasing resistance of the organism to the drug Despite these disadvantages there are well-established cures of subacute bacterial endocarditis by streptomycin Much more rarely and more or less as a last resort sulfadiazine may be added to penicillin or streptomycin or both in the oral dosage of 4 gm initially or 2 gm repeated in two hours followed by 1 gm every four hours until the blood level reaches 10 mg per 100 cc with continuation at that level and finally other antibiotics besides penicillin are worthy of trial in the case of unusual and rare infectious agents not amenable to penicillin

Mention should be made of course of the importance of the best nursing care in the treatment of this disease of patient but optimistic attitude of both doctor and victim during the tedious weeks of therapy and of the early recognition and treatment of complications such as congestive heart failure by the use of digitalis low sodium intake and diuretics In very rare cases cure of infected peripheral blood vessels as in instances of mycotic and arteriovenous aneurysms has been effected by surgical excision

**Differential diagnosis** The four conditions from which it may be difficult to differentiate subacute bacterial endocarditis are (1) active rheumatic heart disease (2) acute bacterial endocarditis (3) infections of other nature with or without chronic valvular disease and (4) blood diseases or severe anemia secondary to some other infection like malaria The duration and average severity of subacute bacterial endocarditis the relative infrequency and unimportance of joint pains or swelling the clubbing of the fingers when present the slight but usually not great enlargement of the spleen the moderate grade of secondary anemia the finding of the *Streptococcus viridans* in the blood stream and particularly the frequency of embolism in an infection not very virulent in nature distinguish this disease with little difficulty from others It is however important to remember that the various conditions cited above may coexist in the same case

## BIBLIOGRAPHY

ACUTE AND SUBACUTE BACTERIAL (INFECTIVE) ENDOCARDITIS  
MALIGNANT ENDOCARDITIS

## Acute Bacterial Endocarditis

- Fox W W "Endocarditis Due to the Hemolytic Para influenza Bacillus" *JAMA* 1935 CV 876
- Gelfman R and Levine S A "Incidence of Acute and Subacute Bacterial Endocarditis in Congenital Heart Disease" *Am J M Sc* 1943 CCIV 324
- Goldburgh A L Baer S and Lieber M M "Acute Bacterial Endocarditis of the Tricuspid Valve" *Am J M Sc* 1942 CCIV 319
- Hurwitz A and Arst D B "Mycotic Aneurysm of the Brachial Artery After Cure of Bacterial Endocarditis" *New England J Med* 1948 CCXXXVIII 903
- Hussey H H et al "Septicemia and Bacterial Endocarditis Resulting from Heroin Addiction Report of Five Cases" *JAMA* 1944 CXXVI 535
- Lion G and Levy Bruhl M "Un cas d'endocardite infectieuse gonococcique avec serodiagnostic positif" *Arch d mal d coeur* 1922 XV 289
- Locke E A "Pneumococcus Endocarditis" *Boston M and S J* 1924 CXCI 913
- Lord F T "Pneumococcus Endocarditis" *New England J Med* 1932 CCVII 767
- Lutgens W F "Endocarditis in Main Line Opium Addicts Report on Eleven Cases" *Arch Int Med* 1949 LXXXIII 653
- Menetrier "Relevé statistique de 400 autopsies de pneumonie" *Bull et mem d soc med d hop d Paris* 1919 XLIII 679
- Merritt W A "Bacterial Endocarditis as Complication of Transurethral Prostatic Resection" *J Urol* 1951 LXV 100
- Mulson F W and Hess H R "Acute Bacterial Endocarditis in Infants" *Am Heart J* 1936 XII 368
- Phipps C "Acute Bacterial Endocarditis" *New England J Med* 1932 CCVII 768
- Rhoads C P "Vegetative Endocarditis Due to the Meningococcus with a Case Report" *Am J Path* 1927 III 623
- Robinson G L and Hartley R "Acute Bacterial Endarteritis" *Brit Heart J* 1951 XIII 106
- Ruiz F R and Garcia P P "Infeccion puerperal y endocarditis maligna" *Rev med latino-am* Buenos Aires 1926 XI 2053
- Russell D S and Fildes P "A Case of Endocarditis in Man Associated with Bacillus Parainfluenzae Rivers 1922" *J Path & Bact* 1928 XXI 651
- Sheldon W H and Golden A "Abscesses of the Valve Rings of the Heart A Frequent But Not Well Recognized Complication of Acute Bacterial Endocarditis" *Circulation* 1951 IV 1
- Thayer W S "On the Cardiac Complications of Gonorrhoea" *Bull Johns Hopkins Hosp* 1922 XXXIII 361
- "Observations on Bacterial Endocarditis" *Weekly Roster and Medical Digest* Philadelphia Mar 14 1925 XX 17
- Warfield L M "Acute Staphylococcus Aureus Endocarditis" *Am Heart J* 1927 II 576
- Williams R H "Gonococcal Endocarditis Study of Twelve Cases with Ten Post mortem Examinations" *Arch Int Med* 1938 LXI 26

## Subacute Bacterial Endocarditis

- Abbott M E *Atlas of Congenital Cardiac Disease* American Heart Association New York 1936
- Baehr G "Glomerular Lesions of Subacute Bacterial Endocarditis" *Tr A Am Phys cians* 1912 XXVII 177
- Blumer G "Subacute Bacterial Endocarditis" *Medicine* 1923 II 105
- Blumgart H L "The Clinical Syndrome of Subacute Bacterial Endocarditis Involving the Right Chambers of the Heart" *M Clin North America* 1933 XVI 881

- Bracht E and Wachter "Beitrag zur Aetiologie und pathologischen Anatomie der Myocarditis rheumatica" *Deutsch Arch f klin Med* 1909 XCVI 493
- Chau E Florey H W Gardner A D Heatley N G Jennings M A Orr Ewing J and Sanders A G "Penicillin as a Chemotherapeutic Agent" *Lancet* 1940 II 6
- Fleming A "The Antibacterial Action of Cultures of Penicillin with Special Reference to Their Use in Isolation of Influenzae" *Brit J Exper Path* 1929 X 276
- Galbreath W R and Hull E "Sulfonamide Therapy of Bacterial Endocarditis Results in 4 Cases" *Ann Int Med* 1943 XVIII 201
- Gelfman H and Levine H A "Incidence of Acute and Subacute Bacterial Endocarditis in Congenital Heart Disease" *Am J M Sc* 1947 CCIV 324
- Goetsch C "Persistent Ostrium Atrio Ventriculare Communis with Bacterial Endocarditis in a Mongolian Idiot" *J Tech Methods* 1938 XVIII 117
- Grant R T Wood J E Jr and Jones T D "Heart Valve Irregularities in Relation to Subacute Bacterial Endocarditis" *Heart* 1928 XIV 247
- Hamman L and Rienhoff W F Jr "Subacute Streptococcus Viridans Septicemia Cured by Excision of an Arteriovenous Aneurysm of External Iliac Artery and Vein" *Bull Johns Hopkins Hosp* 1935 LVII 719
- Heyman J "Subacute Bacterial Endocarditis Successfully Treated with Sulfanilamide Report of Well Established Case 18 Months After Recovery" *JAMA* 1940 CXIV 233
- Kelson S R and White P D "A New Method of Treatment of Subacute Bacterial Endocarditis Using Sulfapyridine and Heparin in Combination" *JAMA* 1939 CXIII 1700
- Lewis C and Grant R T "Observations Relating to Subacute Infective Endocarditis Part 1 Notes on the Normal Structure of the Aortic Valve Part 2 Bicuspid Aortic Valves of Congenital Origin Part 3 Bicuspid Aortic Valves in Subacute Infective Endocarditis" *Heart* 1913 X 21
- Libman E "The Clinical Features of Cases of Subacute Bacterial Endocarditis That Have Spontaneously Become Bacteria Free" *Tr A Am Physicians* 1913 XXVIII 309
- "The Clinical Features of Subacute Streptococcus (and Influenza) Endocarditis in the Bacterial Stage" *M Clin North America* 1918 II 117
- Libman E and Friedberg C K "Subacute Bacterial Endocarditis" Oxford University Press New York 1941
- Martin H F and Adams W L Jr "Bacterial Endocarditis Superimposed on Syphilitic Aortitis and Valvulitis" *Am Heart J* 1938 XVI 714
- Mengert W F "Subacute Bacterial Endocarditis as Complication of Pregnancy" *Am J Obst & Gynec* 1933 XXV 121
- Morrison H "A Study of the Incidence of Subacute Bacterial Endocarditis at the Massachusetts General Hospital" *Boston M and S J* 1927 CXC VII 46
- "Subacute Streptococcus Endocarditis" *New England J Med* 1932 CCVII 770
- O'Keefe C C and Elliott S D "Bacteraemia and Oral Sepsis with Special Reference to Aetiology of Subacute Bacterial Endocarditis" *Lancet* 1935 II 869
- Organ F S and Loston M A "Mixed Infections in Bacterial Endocarditis" *Am Heart J* 1947 XXIII 823
- Oster W "Infectious (so-called Ulcerative) Endocarditis" *Arch Med* 1881 V 44
- "Chronic Infectious Endocarditis" *Quart J Med* 1909 II 219
- Palmer H D and Kempf M "Streptococcus Viridans Bacteremia Following Extraction of Teeth" *JAMA* 1939 CXIII 1788
- Parks H "An Instance of Coronary Embolism in Subacute Bacterial Endocarditis" *Ann Int Med* 1942 XVI 339
- Rost W L and Fischer A E "Subacute Bacterial Endocarditis in Childhood Report of 12 Cases" *Am J Dis Child* 1928 XXXVI 1144
- Schottmüller H "Endocarditis lenta zugleich ein Beitrag zur Artunterscheidung der pathogenen Streptokokken" *Munch med Wchnschr* 1910 LVII 617
- Smith C Sauls H C and Stone C F "Subacute Bacterial Endocarditis Due to Streptococcus Viridans A Survey of the Present Status of the Previously Reported Cures and a Clinical Study of 15 Treated Cases, Including Another Cure" *JAMA* 1942 CXIX, 478

- Touroff A S W and Vessell H Subacute Streptococcus Viridans Endarteritis Complicating Patent Ductus Arteriosus Recovery Following Surgical Treatment. *JAMA* 1940 CXV 1270
- Walser H C "Subacute Bacterial Endocarditis of Streptococcus Viridans Type in Pregnancy with Two Case Reports" *Am J Obst & Gynec* 1928 XV 840
- Weiss H "Relation of Portals of Entry to Subacute Bacterial Endocarditis" *Arch Int Med* 1934 LIV 710
- West G L Sudden Death in a Case of Asymptomatic Subacute Bacterial Endocarditis. *New England J Med* 1931 CCV 675
- White P D and Jones T B Heart Disease and Disorders in New England *Am Heart J* 1928 III 302
- Willius F A Cardiac Clinics LXX Clinic on Subacute Bacterial Endocarditis Affecting an Aged Patient *Proc Staff Meet Mayo Clin* 1940 XV 270

#### Recent References (1944-1950)

- Aubert A and Lerche C Subacute Bacterial Endocarditis in a Child Ten Months Old Successfully Treated with Streptomycin *Am Heart J* 1950 XXXIX 141
- Beyer K H New Concept of Competitive Inhibition of the Renal Tubular Excretion of Penicillin *Science* 1947 XCV 94
- Boger W P et al The Influence of a New Benzoic Acid Derivative [Benemid] on the Metabolism of Para aminosalicylic Acid (PAS) and Penicillin *Ann Int Med* 1950 XXXIII 18
- Boger W P Kay C F and Eisman S H and Yeoman E E Caronamide Compound That Inhibits Penicillin Excretion by Renal Tubules Applied to Treatment of Subacute Bacterial Endocarditis *Am J M Sc* 1947 CCXIV 493
- Burke F G Ross S Walsh H J and McLendon P A "Successful Use of Oral Penicillin in Treatment of Subacute Bacterial Endocarditis Report of Case" *Ann District of Columbia* 1946 XV 22
- Burnell J A and Kirby W M M The Effectiveness of the New Compound Beremid in Elevating Serum Penicillin Concentrations *J Clin Investigation* 1951 XXX 697
- Christie H V Penicillin in Subacute Bacterial Endocarditis Report to Medical Research Council on 269 Patients Treated in 14 Centres Appointed by Penicillin Clinical Trials Committee *Brit M J* 1948 I 1
- Clark W H Bryner S and Rantz L A Penicillin resistant Non hemolytic Streptococcal Subacute Bacterial Endocarditis *Am J Med* 1948 IV 671
- Cunningham W D and Maddox K Cure of Subacute Bacterial Endocarditis During Pregnancy Report of a Case *M J Australia* 1949 II 391
- Dawson M H and Hunter T H "The Treatment of Subacute Bacterial Endocarditis with Penicillin Second Report" *Ann Int Med* 1946 XXIV 170
- Dreher H S Jr Subacute Bacterial Endocarditis Due to Streptococcus Fecalis Failure of Massive Prolonged Penicillin Treatment Case Report with Autopsy *Kansas M Soc J* 1950 LI 119
- Eisman S H Kay C F Norris R F and Boger W P Caronamide as an Adjuvant to Penicillin in the Treatment of Subacute Bacterial Endocarditis *Am J M Sc* 1949 CCXVII 62
- Glaser R J Dankner A Mathes S B and Harford C G "Effect of Penicillin on the Bacteremia Following Dental Extraction" *Am J Med* 1948 IV 55
- Hart F D Morgan A and Lacey B "Brucella Abortus Endocarditis" *Brit M J* 1951 I 1048
- Hewitt W L "Serum Concentrations of Penicillin Following Administration of Crystalline Penicillin G in Peanut Oil and Beeswax" *Am Practitioner* 1947 II 247
- Hoffman W S Volini I F and Hughes J R "Treatment of Subacute Bacterial Endocarditis with Penicillin in Oil and Beeswax" *J Lab & Clin Med* 1947 XXXII 1529
- Hunter T H "Treatment of Subacute Bacterial Endocarditis" *Mod Concepts Cardiovascular Dis* 1946 XV No II
- Hurst W W Gleason A L and Schemm F R "Subacute Bacterial Endocarditis after Operation for Tetralogy of Fallot" *Northwest Med* 1949 XLVIII 763

- Jones M. Subacute Bacterial Endocarditis of Nonstreptococcic Etiology. A Review of the Literature of the Thirteen Year Period 1936-1948 Inclusive. *Am Heart J* 1950 XL, 106
- Kaplan S R, Rosenman R H, Katz L N and Brams W A. Healed Subacute Bacterial Endocarditis. A New Entity. *JAMA* 1949 CXLII 114
- Keefer C ■ Anderson D G and Hewitt W L. End Results in the Treatment of Bacterial Endocarditis. *Tr A Am Physicians* 1948 LXI 112
- Keefer C ■ and Hewitt W L. "Bacterial Endocarditis. Report of End Results in Thirty nine Patients. *Boston M Quart* 1950 I 1
- Nelson S R and White P D. "A Review of 250 Cases of Subacute Bacterial Endocarditis in Boston Hospitals from 1927 to 1939. *Ann Int Med* 1945 XXII 40
- Latscha, B, Lenegre J and Mathivat A. "Un cas d'embolie et un cas d'occlusion ostiale coronariennes au cours de l'endocardite maligne lente. *Arch d mal du coeur* 1949 XLII, 729
- Levy L. and Hull E. "Perforation of the Interventricular Septum in a Case of Subacute Bacterial Endocarditis. *Am Heart J* 1947 XXXIII 856
- Littmann D., and Schaaf R S. Therapeutic Experiences with Subacute Bacterial Endocarditis. Reference to the Failures. *New England J Med* 1950 CCXLIII 249
- Loewe L, Rosenblatt P, Greene H J and Russell M. Combined Penicillin and Heparin Therapy of Subacute Bacterial Endocarditis. *JAMA* 1944 CXXIV 144
- Loewe L, Eiber H B and Altire Werber E. Enhancement of Penicillin Blood Levels Following Oral Administration of Caronamide. *Science* 1947 CVI 494
- M Donald R K. "The Coincidence of Auricular Fibrillation and Bacterial Endocarditis." *Am Heart J* 1946 XXXI 308
- MacLean H and Howell K M. "Two Coexistent Strains of Viridans Streptococcus Isolated from Blood Cultures by Penicillin Sensitivity Tests. *Am J M Sc* 1947 CCXIV 43
- Meads M, Long R V, Pace S H and Harrell G T. Caronamide and Penicillin. *JAMA* 1948 CXXXVIII 874
- Mendelson C L. Pregnancy and Subacute Bacterial Endocarditis. *Am J Obst & Gynec* 1948 LVI 645
- Olinger M G. "Mixed Infection in Subacute Bacterial Endocarditis. Report of Two Cases." *Arch Int Med* 1948 LXXXI 334
- Organ E S and Donegan C K. "The Treatment of Bacterial Endocarditis. *Ann Int Med* 1950 XXXII 1099
- Paul O, Bland E F and White P D. "Bacterial Endocarditis. Experiences with Penicillin Therapy at the Massachusetts General Hospital 1944-1946." *New England J Med* 1947 CCXXXVII 349
- Pulaski E J and Connell J F Jr. Procaine Penicillin G for Aqueous Injection. A Study of Blood and Urine Levels. *New England J Med* 1949 CCXLI 514
- Roston E ■ and Stollerman G H. Procaine Penicillin in the Treatment of Subacute Bacterial Endocarditis. *Am Practitioner* 1949 IV 102
- Salazar Mallen M, Lozano Hube E and Brenes M. Comparative Study of Blood Cultures Made from Artery Vein and Bone Marrow in Patients with Subacute Bacterial Endocarditis. *Am Heart J* 1947 XXXIII 692
- Saphir O. "Myocardial Granulomas in Subacute Bacterial Endocarditis. *Arch Path* 1946 XLII 574
- Saphir O, Katz L N and Gore I. The Myocardium in Subacute Bacterial Endocarditis. *Circulation* 1950 I 1155
- Spies H W, Dowling, H F, Lepper M ■ and others. "Aureomycin in Treatment of Bacterial Endocarditis. Report of Nine Cases Together with Study of Synergistic Action of Aureomycin and Penicillin in One Case." *Arch Int Med* 1951 LXXXVII 66
- Taniguchi T and Murphy F D. "Mural Bacterial Endocarditis Produced by Proteus. *JAMA* 1950 CXLIII 427
- Traub E F, Carter J B, Gumbiner S H and Hench W N. "Bacterial Endocarditis in the Elderly. A Report of 94 Autopsied Cases. *Geriatrics* 1949 IV 205
- Zeman F D. Subacute Bacterial Endocarditis in the Aged." *Am Heart J* 1945 XXIX, 661



## CARDIOVASCULAR SYPHILIS

---

**Introduction** This is another chapter which we may justifiably hope and expect to become obsolete during the next generation since already great progress in the reduction of cardiovascular syphilis has been actually demonstrated to the author and his contemporaries during the past generation by means of the prevention of syphilis itself in the first place its earlier recognition and more adequate initial treatment in the second place and its better therapy even in its later or tertiary phase in the third place

In every chapter that has preceded the present one a considerable revision has been necessary as the result of the rapid strides of medical progress in the past seven years since the last edition of this book. Even more dramatically has progress been made in the subject of the present chapter in the way of preventive medicine. And yet despite this advance syphilis continues to be after rheumatism the second most common and important cause of infectious cardiovascular disease. By the time the diagnosis of cardiovascular syphilis is made it is in most cases a very serious condition. Fortunately however it is a preventable disease and already in many parts of the world it is on the wane and no longer common. In New England two decades ago it was found to make up 4 per cent of a large series of cases of cardiovascular disease (White and Jones 1928) being more frequent in general hospital practice than in private practice now however it makes up less than a quarter of that figure (that is less than 1 per cent). Among the Negroes in the southern part of the United States on the other hand it is still a common though decreasing cause of cardiovascular disability and death being a prime factor in about 20 per cent of cardiac patients even there it is less frequent than the factor of hypertension. In a series of 414 Negroes in Texas with cardiovascular disease over twenty years ago syphilis was the chief factor in 32 per cent and hypertension in 50 per cent (Stone and Vanzant 1927) there too however the recent public health campaign gives promise of a reduction in cardiovascular syphilis such as has occurred elsewhere.

It is a very interesting fact as yet unexplained that syphilis damages the

aorta more than other arteries or the myocardium. Cardiovascular syphilis consists primarily therefore of aortitis with or without secondary effects on the heart. Infrequently it means myocardial disease or involvement of great vessels other than the aorta such as the femoral, carotid and pulmonary arteries.

In a series of 50 000 consecutive autopsies in Minnesota over a period of thirty seven years beginning in 1910 syphilitic heart disease not including uncomplicated aortitis dropped in incidence from a maximum of 2.04 per cent at the beginning to 0.23 per cent at the end in individuals 40 years of age or older (Clawson 1950). The general incidence of syphilitic cardiac deaths (0.83 per cent) in this autopsy material is now less than that of deaths from calcific aortic valvular disease (1.3 per cent). Syphilitic aortic insufficiency ranked first in the manner of death in Clawson's series of cases of syphilitic heart disease (58.5 per cent). Deaths due to rupture of a syphilitic aneurysm were second with 21 per cent and those due to narrowing of the coronary orifices third with 18.9 per cent. There were relatively few cases of gumma of the myocardium.

In a series of 9 807 necropsies in Italy the incidence of heart disease due to syphilis was found to be 2 per cent (Venzoni 1939). In a Cincinnati hospital with a large proportion of Negro inmates however the incidence of syphilitic aortitis in autopsies from 1926 to 1937 inclusive was reported to be much higher (at least 9.1 per cent) (Gelperin 1940) while in the Philadelphia General Hospital the percentage dropped from 9.2 in the years 1927 to 1930 to 5.6 in 1935 to 1937 (there was a majority of Negro cases) (Welty 1939).

**Etiology Cause.** The organism responsible for cardiovascular syphilis the *Treponema pallidum* was discovered in a diseased aorta in 1906 (Reuter) but long before the discovery of the actual causative agent in syphilis the connection between that disease and aortitis was known and for several centuries the production of aneurysms by syphilis was suspected (Pare 1575, Lancisi 1724, and Morgagni 1761). Gummata long known to be of syphilitic origin were early found in the heart itself.

Although it is probable that the spirochete of syphilis invades the heart and aorta early in the disease at the same time that it invades other organs, actual disease of aorta and of heart due to syphilis is as a rule first demonstrable either by symptoms or by signs only a good many years after the primary lesion (chancre). Twenty years elapse on the average between the onset of the infection and its evident involvement of the cardiovascular apparatus but there are wide variations, the intervals ranging from a few weeks to 30 or 40 years. Except in rare cases clear evidence is wanting that there is any important involvement of the heart or aorta during the primary or secondary stage (that is during the first few weeks or months) of the syphilitic infection. Most reports to the contrary are unsatisfactory. Years ago because of the lateness of this evidence of infection aortitis and aneurysms were classed along with tabes dorsalis and general paresis as fourth stage or parasyphilitic lesions.

that is the end result of the infection that had become inactive while gummata when they were found were considered manifestations of the tertiary stage still active. Now we know that all these processes are but different evidences of the syphilitic infection appearing late but still active, a few aneurysms are relatively inactive scarred lesions but such unprogressive aneurysms are uncommon.

There is obviously some sort of affinity between the treponema and the aortic wall just as there is between this organism and the central nervous system in certain individuals, what it is we do not yet know. Most cases of acquired syphilis do not however develop cardiovascular disease at least 90 per cent never show clinical or pathologic evidence of such involvement.

Congenital syphilis as well as acquired syphilis may cause cardiovascular disease but the congenital syphilitic type is not common. The simple presence of treponemata in the heart muscle of a syphilitic fetus or child (a common finding at postmortem examination) does not constitute syphilitic heart disease there must be appreciable tissue reaction or destruction in addition. This is well illustrated by a report of a study of 939 children with congenital syphilis (McCulloch 1930) 498 of these children were over two years of age and only 5 showed any signs of cardiovascular disease and in them such heart disease was clearly of rheumatic nature of the other 441 children who were under two years of age 32 died but only 3 of these were found to have syphilitic heart disease while none of the 409 survivors showed any signs whatsoever of cardiovascular syphilis.

*Age* Because of the possibility of cardiovascular involvement by syphilis in fetal life and of the possible acquisition of the infection relatively late in life the age at which cardiovascular syphilis may show itself clinically or at autopsy varies from birth to old age. The usual age of clinical manifestation however is in the late forties the large majority of cases come to notice between the ages of 40 and 55 years. In one series of 95 cases there was one patient less than 10 years old there were four between the ages of 20 and 30 eleven between 30 and 40 twenty five between 40 and 50 thirty three between 50 and 60 twenty between 60 and 70 and one over 70 (White and Jones 1928). Among Negroes the age at which cardiovascular syphilis becomes evident is younger nearer 40 than 50 frequently in the thirties and even rarely in the twenties. In recent years two more cases with syphilitic thoracic aneurysms who were under the age of 30 years have been reported (Evans 1941).

*Sex* The male sex has far more cardiovascular syphilis than has the female. In the series of 95 cases mentioned above 78 were male and 17 were female a ratio of almost 5 to 1 (White and Jones 1928). In another series of 70 cases the ratio was 6 to 1 (Nichols 1940). In Moore's series the ratio was about 2 to 1 (Moore et al 1932) and in a more recent series of 199 cases of syphilitic aortitis found among 9 807 necropsies (Venzoni 1939) there were 164 men and 34 women (5 to 1). This is undoubtedly due largely

to the far greater male exposure to syphilis and to the factor of greater physical activity

*Other factors* Other known etiologic factors in cardiovascular syphilis are race and social and economic status. These are very important since the members of most of the less civilized races are far more subject to syphilis once it is introduced among them than are those of civilized races where social customs and measures of prevention and early treatment afford at least a certain amount of protection. Even in a civilized community the percentage of cardiovascular syphilis is greater among the inhabitants of lower social and economic order. In Moore's series it was about twice as common in Negro as in white patients (Moore et al. 1932). A large percentage of the population of some half civilized peoples is found to be infected with syphilis; what percentage of those develop cardiovascular disease due to this infection we do not know because of the lack of accurate statistics. We might at first thought believe that cardiovascular syphilis would be very common in such peoples but that is not always the case as found out in Arabia by Paul Harrison (personal communication 1940) who encountered only very rare cases of aortic aneurysm or aortic regurgitation in an active medical service over many years in a country riddled with syphilis. It seems likely that a relative immunity so far as serious effects are concerned can be acquired in countries where syphilis has long been almost universal and but little treated. In Uganda however cardiovascular syphilis is said to be common comprising over half of all heart disease among Africans (Williams 1938).

*The more laborious occupations* are also almost certainly a cause for early appearance and rapid evolution of aortic changes due to syphilis because of the greater physical strain produced thereby.

*The factor of early and satisfactory treatment of the original syphilitic infection* is undoubtedly one of much importance as it concerns the later development of cardiovascular disease of syphilitic origin in civilized communities at least. This is only now becoming evident since it is only in recent years that antisyphilitic therapy has been planned and administered in any satisfactory degree to the majority of patients. An example of this effect is the decrease in the incidence of cardiovascular syphilis both relatively and absolutely seen at the Massachusetts General Hospital in recent years. In 1914 Cabot reported 12 per cent of a group of 600 cardiac cases as due primarily to syphilis; in 1928 White and Jones reported 5 per cent of a series of 880 cardiac cases as primarily or secondarily of this type in the same clinic while in 1949 we have found only 1.5 per cent among 1 000 cardiac cases. Another interesting comparison in this hospital is that of the incidence of the diagnosis of aneurysm of the aorta in the ten year period of 1900 to 1909 inclusive (113 among 51 875 cases or 0.2 per cent) with that in the ten year period of 1925 to 1934 inclusive (only 61 among 75 184 cases or 0.08 per cent despite the improved roentgenologic facilities for diagnosis). In Baltimore in 1932 Moore and his associates stated that not one of 117 patients with

early syphilis who received three or more courses of arsphenamine and treatment with mercury during periods between the courses presented any evidence of cardiovascular involvement during the period of observation (up to nine years after the infection) while 24 of 285 patients followed during this same period of observation who had received less than this amount of treatment were observed to acquire syphilitic aortitis aneurysm or aortic regurgitation. Adequate treatment for early syphilis almost certainly protects the majority of patients so treated against subsequent cardiovascular syphilis. Various procedures are now in progress in the use of penicillin in the rapid treatment of early syphilis for example 600 000 units of procaine penicillin daily for ten days (Kossmann personal communication 1949)

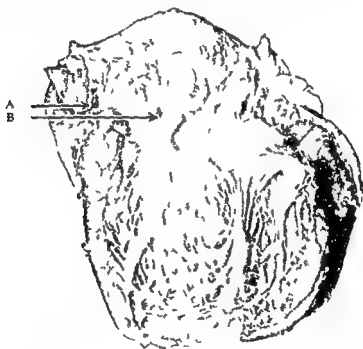


FIG 89 Photograph showing syphilitic aortitis with marked narrowing of the mouth of the right coronary artery (B) the mouth of the left coronary artery (A) is slightly narrowed Compare this with Figure 147 (Jores Arterien Courtesy of Julius Springer Berlin)

**Pathology** Cardiovascular disease due to syphilis is of three main types

1 The first and commonest type is the result of *destruction of the media of arteries*. The exact pathogenesis of this lesion is not known in the aorta it is thought to result from obliterative endarteritis of the vasa vasorum. It is most evident in the ascending portion of the aorta where the intima becomes pale and wrinkled due to the destruction of the media below it (Figure 89). The aortic wall is thus seriously weakened and loses its elasticity stretches and dilates. The intima is thickened becomes atheromatous and may ulcerate

though ulceration is less common than in the case of primary atheroma. The spirochete of syphilis may sometimes be found in the diseased aorta.

Three important developments of this destructive syphilitic aortic process may occur if no one of these is found as sometimes happens the condition then remains clinically unimportant. These three developments are— (1) stretching of the aortic wall to give rise either to a diffuse or spindle shaped dilatation or aneurysm or locally to a saccular aneurysm (2) an involvement of the aortic valve to deform it and to cause aortic regurgitation and (3) a narrowing of the mouths of important branches of the aorta by an extension of the process itself.

(a) *Aortic aneurysms* like syphilitic aortitis itself most commonly involve the ascending portion of the aorta less often the aortic arch and least often the descending portion in thorax or in abdomen. They are only an occasional accompaniment of aortitis being found in 10 per cent or fewer of the cases but they are serious because of the pressure they often exert on surrounding structures and because of their tendency to rupture into pleural cavities pericardial sac bronchi or trachea esophagus mediastinum or even into other great vessels (pulmonary artery or superior vena cava). Aneurysms are still rarer accompaniments of other conditions such as atherosclerosis senile ectasia trauma or bacterial endarteritis. They are discussed further in Chapter 28 of this book.

(b) *Aortic valve disease with regurgitation* is a much more common accompaniment of syphilitic aortitis than is aneurysm occurring in one quarter to one half of the cases diagnosed clinically though rarely early in the disease. It was found in 36.5 per cent of the 126 cases of syphilitic aortitis examined post mortem by Clawson and Bell (1927) and in 27 per cent of the series of cases of cardiovascular syphilis of Moore and his associates (1932) which in turn made up 10 per cent of a clinical series of 6 420 patients with various forms of late syphilis. It is due to a downward extension of the aortitis to involve primarily the commissures of the valve. The inflammatory process widens the commissures and by separating the cusps produces regurgitation (Figure 131 shown on page 686) this is the reverse of the rheumatic effect which unites the cusps at the commissures to cause stenosis rather than regurgitation. Extension of the syphilitic process may further damage the valve cusps themselves and cause their retraction or adhesion to the sinuses of Valsalva. A very interesting finding is a rather rare eventration of one of the aortic valve cusps giving rise to a striking loud high pitched musical aortic diastolic murmur with thrill (Bellet et al 1939 Nichols 1940). A weakening of the aortic valve ring with stretching often comes with aortitis and is probably more commonly the cause of aortic regurgitation than is valve deformity per se. Thus aortic regurgitation so frequently complicating syphilitic aortitis may result either from this stretching alone or from damage to the valve or from both factors. The other heart valves are not affected by the syphilitic process directly except as the anterior cusp of the mitral valve may be somewhat involved or deformed by spread of the inflammatory

reaction down over it from the aortic valve or by retraction of the damaged aortic valve

(c) *Narrowing of the mouths of the branches of the thoracic aorta* by the inflammatory syphilitic process is an important and not infrequent complication of the aortitis. It may even advance to the stage of actual occlusion. *Coronary involvement of this nature* (Figure 89) is particularly serious and accounts in large part for the angina pectoris and especially for the sudden death so often occurring in patients with syphilitic aortitis. It was found in 25 per cent of the series of 126 autopsied cases of syphilitic aortitis of Clawson and Bell (1927) and in over half (105 out of 199) of the autopsied cases of Venzoni (1939). Although the coronary arteries beyond their mouths are usually not involved in the process they may rarely be the seat of a syphilitic mesarteritis with narrowing and obstruction or even aneurysmal dilatation (Seydel 1935). Other arteries—the innominate carotid subclavian and intercostal—may also be more or less occluded at their mouths in syphilitic aortitis especially if there be in addition aneurysmal dilatation which compresses these arteries. Such obstruction may lead to decrease and delay of one or both of the carotid or radial pulses and rarely to their obliteration with development of a collateral circulation to head or arms.

Other arteries besides the aorta and coronary arteries may be attacked by the syphilitic process with thickening of wall thrombosis and occlusion or with stretching of the weakened wall and aneurysmal development. There may be aneurysms anywhere in the body. In themselves aneurysms exert little or no strain on the heart the strain comes if they perforate into veins (arteriovenous aneurysm) or if in the case of the aorta the coronary arteries are obstructed or the aortic valve is deformed. Sclerosis of the pulmonary artery and its branches following syphilitic involvement of the bronchi and causing right ventricular failure and marked cyanosis (black cardiacs) was described in 1901 (Ayerza as quoted by Arnaga in 1912—see bibliography of Chapter 20) but such a syphilitic sequela is excessively rare the great majority of cases of cor pulmonale with right heart failure and marked cyanosis are not syphilitic (see Chapter 20).

2 The second type of syphilitic involvement after that of the arteries is a *diffuse inflammatory reaction in the myocardium* with the presence of spirochetes (Warthin 1925 Magill 1935). Some cases of sudden death have shown this syphilitic myocarditis, but it is an infrequent manifestation of cardiovascular syphilis. Rupture of a papillary muscle due to syphilitic myocarditis has been noted but it is exceedingly rare.

3 The third type of cardiovascular syphilis is also rare and consists of the *invasion of the heart by gummata*. These localized reactions to the presence of spirochetes may be situated anywhere in the heart—atrial walls ventricular walls or septum. If they occur high in the interventricular septum they may involve the specialized conduction system of the heart—the atrioventricular bundle of His or its branches—and produce heart block of one type or another. Gummata in the myocardium were found in only 3 of the 126

autopsied cases of Clawson and Bell's series (1927) Myxoid formations in the myocardium consisting of rounded translucent nodules have also been reported as a syphilitic lesion (Warthin 1916)

**Symptoms** Cardiovascular syphilis is often symptomless not only in its early stages but sometimes even when it has become far advanced It produces symptoms chiefly (1) by its involvement of the aortic valve which causes heart strain and eventual failure or (2) by its narrowing of the coronary artery mouths or walls to cause angina pectoris and even very rarely acute myocardial infarction (Burch and Winsor 1942) or (3) by the pressure of aneurysmal dilatation on surrounding tissue to cause pain or to obstruct blood flow in other vessels to block esophagus or air passages or to occasion hoarseness by involvement of the recurrent laryngeal nerve with paralysis The aortitis itself is almost always symptomless but sometimes a more or less constant dull ache high under the sternum has been ascribed to it even though there be no definite aneurysm

The earliest and commonest symptoms associated with cardiovascular syphilis which usually means aortitis are less commonly angina pectoris and more commonly paroxysmal dyspnea with or without cardiac asthma or frank pulmonary edema Either one or both may be present with no other symptoms at all or all the symptoms of congestive failure—more or less constant dyspnea weakness and pulmonary and systemic edema—may supervene to replace the angina pectoris or to appear at the very onset of evident trouble Sometimes pallor and loss of strength and weight also appear early in the disease

Sudden death is quite common in cardiovascular syphilis with or without preceding symptoms it was reported as having occurred in 39 of the 199 cases (20 per cent) in the series of Venzoni (1939)

**Signs** There may be no signs whatsoever of cardiovascular syphilis by any method of examination and the condition may be discovered only at postmortem examination Dilatation of the aorta which occurs after the process has advanced considerably may also escape attention for some time even after symptoms have appeared unless careful roentgenologic study is made Even when careful roentgenologic examination is carried out it is not possible to recognize early or slight syphilitic aortitis thereby for aortic dilatation and secondary calcification are after all rather late effects and actual dilatation of the first few centimeters of the aorta (a common site of syphilitic aortitis) may be present with no evidence by roentgen ray because the aortic shadow at its root is buried in that of the heart in all roentgenologic views and positions as carried out routinely However by the injection of a contrast medium such as Diodrast the root of the aorta can usually be delineated in doubtful cases

Later on when the process has become extensive and has advanced to the stage of aneurysmal formation of aortic regurgitation or of coronary obstruction ordinary methods of clinical examination may reveal it but by that time the situation may be hopeless Keen observation and careful study must



always be carried out when there is a suspicion of aortitis. Since symptoms and signs often appear only when the disease is advanced, however, it will rarely be possible to pick up the early cases in spite of routine periodic examinations. Routine examinations nevertheless, especially of those individuals with a history of syphilitic infection, will sometimes reveal trouble that may be amenable to treatment before any symptoms have forced the patient to consult medical advice. The value of these examinations should be universally realized.

With aortitis alone or with aortic aneurysm without aortic regurgitation or coronary obstruction, the heart remains normal in size without murmurs, but when aortic valve disease develops with increasing regurgitation, the heart enlarges rapidly and may eventually increase to enormous size to produce the typical *cor bovinum*. With a considerable valve defect, a loud aortic diastolic murmur develops, louder than is found as a rule in rheumatic aortic valve disease and often heard best at the right of the upper sternum. A moderate to loud aortic systolic murmur also is usually heard there (due to the aortic dilatation). The heart sounds are masked. A functional mitral diastolic murmur (Austin Flint) is common, and the peripheral pulse becomes water hammer in character along with the appearance of the so-called capillary pulse. Stenosis does not complicate the aortic regurgitation of syphilitic aortitis, although aortic stenosis, probably of rheumatic origin, has been encountered along with syphilitic aortitis (for example, three such cases noted by Cabot, 1926). A curious loud high pitched musical character may be imparted to the aortic diastolic murmur with development of a palpable thrill when, as already noted above, there is an eventration of one of the valve cusps (Bellet et al., 1939; Nichols, 1940). It is to be remembered that the aortic regurgitation of syphilitic aortitis may begin gradually and at first may be but slight; hence it is possible in some cases to find only a slight to moderate aortic diastolic murmur without a Corrigan pulse.

There are three signs that have sometimes been adduced as evidence of early syphilitic aortitis before the development of aortic regurgitation or of well marked aortic dilatation. They are (1) an aortic systolic murmur, (2) accentuation of or a tympanic or metallic note to the aortic second sound, and (3) increased retrosternal percussion dullness. These signs are all very unreliable, the first two being much more common in cases of aortic sclerosis with past or present hypertension, and the third being found only when there is marked aortic dilatation or a widening of or disease in the mediastinum.

The serum reaction for syphilis (Wassermann, Kahn, Hinton) is generally positive and strongly so in cardiovascular syphilis, sometimes in approximately 15 per cent of the cases it is negative. The Hinton reaction is more sensitive than the Wassermann test. It must be remembered, however, that syphilis with a positive Wassermann reaction may be present as an incidental infection complicating chronic valvular disease or angina pectoris which is not of syphilitic origin. This fact accounts, I believe, for a gross overestimation of

syphilitic aortitis as a cause of angina pectoris in some parts of the world in days gone by

The essential evidence of syphilitic aortitis is most commonly presented by roentgen ray examination the bulging of the thoracic aorta (especially the ascending portion and the arch) without other adequate reason (for example hypertension) affords the essential clue (Figure 146 page 770) The electrocardiogram remains normal until the heart enlarges as the result of aortic regurgitation with the development then of the pattern of left ventricular hypertrophy and dilatation (see Chapter 9) or until the coronary circulation is interfered with when one of the many patterns of coronary heart disease may appear

**Course and prognosis** The onset of cardiovascular syphilis is very slow and insidious When aortitis has become established years after the initial lesion and has come to light because of the symptoms or signs it has produced the course is often difficult and the prognosis is often poor Sometimes however treatment helps a good deal in relieving symptoms and in retarding the progress of the disease Spontaneous cures or rather cessation of symptoms without further development of signs are also seen Not infrequently in the course of a few months to several years after the discovery of the trouble death occurs suddenly with or without preceding angina pectoris or it may result from congestive heart failure some complicating infection or cerebral lesion or rarely rupture of an aneurysm Sometimes death comes quickly even in a few weeks sometimes it is postponed for ten to twenty or more years The average duration of life from diagnosis to death used to be about three years it has been increasing steadily since more effective therapy has been carried out One of the most important factors of all in controlling prognosis is the degree of physical activity of the patient the more strenuous the life in this respect the shorter it will be a relatively quiet existence undoubtedly prolonging life This fact is a prime reason for the very serious prognosis of cardiovascular syphilis among the Negro laborers Of 124 cases of syphilitic aortic regurgitation followed personally by Blackford 57 died within one year of the discovery of the lesion 27 more died during the next two years 17 were known to be alive after three years and 8 were still alive after five years (Blackford personal communication 1936) In all probability the factor of hard physical work is more important than that of race in this regard although it is true that the relative neglect of treatment may enter also

The effect of energetic specific treatment even of this late syphilis of aorta and heart on prognosis has been in the main distinctly favorably as has been demonstrated by a number of authorities (Moore et al 1932 Padgett and Moore 1935 Buch 1945 Webster and Reader 1948) A study of 116 patients (103 men and 63 women) with late syphilitic cardiovascular lesions showed the following relative survival periods for well treated moderately treated and poorly treated cases 71 months 57 months and 16 months respectively (Buch 1945) Webster and Reader studied the microscopic

sections of the aortas of 45 patients with gross evidence of syphilitic aortitis at postmortem examination with relation to the effect of treatment. The patients were divided into untreated, inadequately treated and adequately treated groups, the criterion of adequate treatment being a minimum of at least 20 arsenical and 20 bismuth injections, only three of 19 patients adequately treated showed any activity of the process while all 9 untreated cases showed active cellular infiltration of the aorta.

Sudden death is occasionally the result of an undiagnosed syphilitic involvement of aorta or heart without previous symptoms or signs. The medical examiner or coroner establishes the cause of death. If such cases were added to those in whom the diagnosis has been made before death, the statistics of the total number of cases of cardiovascular syphilis in the community would be slightly increased but probably by not more than a very few per cent at most, depending of course on the thoroughness of medical examination and care and of postmortem examinations in that particular community.

The prognosis may be made worse in rare cases by too vigorous therapy. Heart failure and even death have followed directly in a few cases from overzealous efforts to cure.

**Complications.** The important complications of cardiovascular syphilis have already been referred to under the heading of pathology—aneurysms, angina pectoris, coronary occlusion (not coronary thrombosis) and congestive heart failure. Other types of heart disease or of vascular disease may be present in particular, arteriosclerosis of aorta or of coronary arteries, chronic rheumatic valvular disease, hypertension and uncommonly subacute bacterial endocarditis. A confusing picture is sometimes presented by the aorta when syphilis and atheroma are present together; this not infrequently happens in older patients. Syphilitic aortitis predisposes to sclerosis, elongation and tortuosity of the aorta but apparently not much to dissecting aneurysms. Pericarditis is a rare complication of aortitis and is not a part of the syphilitic picture. Important cardiac arrhythmias are also uncommon, especially atrial fibrillation. Premature beats are occasionally seen and are frequently followed by pulsus alternans if the left ventricle is weak. Heart block, either atrio-ventricular or intra-ventricular in type, is found now and then but it is rarely of high grade; complete atrioventricular block and bundle branch block are much more commonly the result of nonsyphilitic coronary disease.

Central nervous system syphilis complicates cardiovascular syphilis in from 20 to 30 per cent of the cases, while cardiovascular syphilis has been reported in 20 to 25 per cent of cases of general paresis and in from 15 to 50 per cent of cases of tabes dorsalis.

**Treatment.** With the advent of penicillin the discussion of the treatment of cardiovascular syphilis needs radical revision. It resembles that of subacute bacterial endocarditis in that a really specific and curative therapy of the active disease process has been introduced though leaving behind it, as in the case of subacute bacterial endocarditis too, a scarred heart but it differed markedly in the past in that there already existed for cardiovascular syphilis

reasonably good therapy. Although penicillin may eventually completely replace the heavy metals, namely arsenic, bismuth and mercury, in the treatment both of syphilis initially and of its sequel of cardiovascular disease, I shall retain here for use even if only supplementary and for historic interest during transition much of the detail of the therapy presented in the last edition of this book.

Current experience has established the value and safety of penicillin therapy of cardiovascular syphilis and therefore such treatment is more and more replacing that with the heavy metals. At first it was feared that the speedy resolution of the active disease in aorta and heart might have serious consequences in the way of weakening the wall and of inducing the Jarisch-Herxheimer reaction. Hence at first very small doses of penicillin were administered, for example, 500 to 3 000 units, but as time went on it was discovered that much larger amounts could be safely and effectively given, 25 000 to 100 000 units (Tucker and Farmer 1947; Moore et al. 1948; Kossmann and Flaum 1948; Porter 1948). But apparently the coexistence of neurosyphilis, especially general paresis, does increase the threat of the Herxheimer reaction (Moore et al. 1948). Several authorities have recommended for the adequate treatment of cardiovascular syphilis a total dosage of from 5 000 000 to 15 000 000 units of sodium penicillin given in aqueous solution by intramuscular injection over a period of about three weeks, for example 40 000 units every three hours for 150 doses (Kossmann and Flaum 1948). Procaine penicillin in the dosage of 600 000 units once daily in the buttocks or 300 000 units twice daily for ten days to two weeks can be more conveniently administered.

For particular symptoms special treatment is indicated, as in the use of the nitrites for angina pectoris or digitalis and if necessary diuretics for congestive failure and of hypnotics and narcotics for insomnia and aneurysmal pressure pains. For intractable angina pectoris and pains due to pressure or erosion by an aneurysm, paravertebral sympathectomy or alcohol injection has proved of much value (see Chapter 21). Total thyroidectomy is contra-indicated.

It is regarding specific antisyphilitic therapy with the heavy metals that there was much disagreement in the past. Some were for forcing it vigorously in the hope of stopping the progress of the disease; others would give none for fear of weakening the aortic wall or myocardium by too rapid a destruction of treponemata and resolution of inflammatory tissue with resultant heart failure or increased stretching of aortic wall. The wisest course undoubtedly rested between these two extremes—namely the careful long-continued administration of a moderate amount of antisyphilitic drugs, determined in each individual case by the condition and needs of that case. In the presence of congestive failure antisyphilitic therapy was withheld until treatment of the failure had been successful, but today penicillin can be given concurrently under careful supervision.

The technic in the use of the heavy metals which has been successful in

many cases of cardiovascular syphilis in the past may best be quoted directly from the several paragraphs concerned in the last edition (1944) of this book. The only debatable point concerns the addition of potassium iodide which although traditional has been omitted by a number of authorities without detracting from the success of the treatment. Incidentally it has not been necessary to add potassium iodide to penicillin in the new therapy of syphilis. It seems reasonable therefore to place in brackets the reference to potassium iodide in the quoted paragraphs.

The following procedures for the administration of specific therapy in cardiovascular syphilis although by no means the only methods that may be employed have proved by extensive experience to be satisfactory. If the diagnosis is certain or reasonably sure and congestive failure or serious renal and hepatic disease are not present therapy is begun with mercury or preferably bismuth and potassium iodide. It is preferable to begin with bismuth in the form of an insoluble salt (the subsalicylate) by intramuscular injection in the dosage of 0.1 gram (1½ grains) every four days for four weeks and then 0.2 gram (3 grains) weekly for another eight weeks. [Simultaneously with the bismuth potassium iodide should be given by mouth 2.0 to 3.0 grams (30 to 45 grains) three times daily.] The drugs must be decreased in dosage or stopped if toxic symptoms arise. Such toxic symptoms consist chiefly of salivation in the case of bismuth [and of urticaria, erythema, lachrymation and corjza in the case of potassium iodide]. Also there must be a pause in the specific antisyphilitic therapy if congestive heart failure supervens. except that either of the two excellent mercury diuretics Salysrgan (Mersalyl) or Mercupurin (Novum) may be injected intravenously or intramuscularly in the dosage of 2 cc weekly or once every few days until the congestion is cleared up. Such therapy acts however in combating the heart failure rather than in controlling the cardiovascular syphilis.

At the end of this first course of twelve weeks arsenic should be cautiously added to the therapy if the condition of the patient warrants as it usually does. Mapharsen in twelve weekly intravenous injections beginning with 0.02 gram and increasing gradually to a maximum dose of 0.04 gram is desirable if possible. Bismarsen (bismuth arsphenamine sulphonate) may be given instead of Mapharsen to the less favorable that is the sicker patients by intramuscular injection of 0.1 gram every five days increasing to 0.2 gram at a dose for a period of twelve weeks.

At the end of this second course one should return without pause to the therapy used in the first course. Injections of an insoluble bismuth salt [along with potassium iodide]. These two courses should then be alternated every three months for a minimum period of two years. After that one course of bismuth followed by one course of Mapharsen or Bismarsen should be given annually for the duration of the patient's life.

Such antisyphilitic therapy as has been outlined above may now and then yield striking results with decrease or disappearance of angina pectoris or of heart block or with cessation of growth or even decrease in size of aorta or aneurysm. In many cases it merely retards the progress of the disease. Rarely it does harm but discrimination in the selection and administration of the therapy obviates almost all danger. Taking everything into consideration prolonged but not rapid specific

therapy of cardiovascular syphilis is well worth while. Not only is life prolonged by adequate therapy (by several years in Moore's series of cases of aortic aneurysm and syphilitic aortic regurgitation as compared with control cases—Moore et al 1932 and Padgett and Moore 1935) but symptoms are decreased and disability is lessened.

The most important consideration of all however with respect to cardiovascular syphilis is that it is a preventable disease. Early and thorough treatment of the initial syphilitic infection should practically wipe out syphilitic aortitis and its sequelæ.

**Differential diagnosis.** Cardiovascular syphilis chiefly in the form of aortitis is to be differentiated particularly from angina pectoris of nonsyphilitic origin from chronic valvular disease of rheumatic nature especially affecting the aortic valve from a kinked or tortuous aorta due to extensive atherosclerosis or to a high position of the diaphragm with horizontally placed heart simulating a dilated aorta in the roentgenologic anteroposterior view but easily identified in the oblique views from mediastinal tumors which may simulate aortic dilatation or aneurysm by physical examination and roentgen ray and from hypertensive arteriosclerotic heart disease with aortic dilatation aortic regurgitation and congestive failure. Very rarely there may exist acute gummatous myocarditis simulating acute myocardial infarction (Reifenstein 1936). All signs and symptoms including the Wassermann and Hinton reactions must often be considered together before a definite diagnosis can be arrived at. Sometimes even then it is impossible to differentiate syphilitic aortitis from these other conditions. The only fairly certain sign is that of the presence of an aneurysm of the thoracic aorta in the male. Aneurysms of the abdominal aorta are generally arteriosclerotic as are also rare thoracic aneurysms in old women. The earliest stage of aortitis cannot be diagnosed clinically the aorta being at that time of normal size and shape.

Aortic syphilis has been and in fact is still being overdiagnosed in the presence of the combination of angina pectoris or aortic regurgitation and of a positive serologic reaction or a history of syphilitic infection. In truth angina pectoris is uncommonly due to syphilis even though syphilis is present in the case and also in some parts of the world where rheumatic heart disease is common. Rheumatic aortic regurgitation and syphilis with or without aortitis may be present in the same patient.

## BIBLIOGRAPHY

### CARDIOVASCULAR SYPHILIS

- Beckh W. The Serologic Reaction in Cardiovascular Syphilis. *Am Heart J* 1943 XXV 307.  
 Bell E. T. Frequency with Which Syphilitic Lesions are Encountered in Postmortem Examinations. *Arch Path* 1938 XXVI 839.  
 Bellet, S. et al. "Loud Musical Diastolic Murmurs of Aortic Insufficiency." *Am Heart J* 1939 XVIII 483.

- Blackford L M "Syphilitic Aortic Insufficiency Cases of Unusual Duration" *J M A Georgia* 1935 XXIV No 9
- Burch G E and Winsor T "Syphilitic Coronary Stenosis with Myocardial Infarction" *Am Heart J* 1942 XXIV 740
- Cabot R C "The Four Common Types of Heart Disease An Analysis of Six Hundred Cases" *JAMA* 1914 LXIII 1461
- Facts on the Heart* W B Saunders Co Philadelphia 1926
- Clawson B J "Syphilitic Heart Disease" *Urol & Cutan Rev* 1941 XLV 219
- Clawson B J and Bell E T "The Heart in Syphilitic Aortitis" *Arch Path and Lab Med* 1927 IV 922
- Evans B "Syphilitic Thoracic Aneurysm in Young Adults" *Brit M J* 1941 I 851
- Gelperin A "The Incidence of Syphilitic Aortitis in a Representative Municipal Hospital" *Am Heart J* 1940 XX 340
- Lancisi J M *De novissime observatis abscessibus* Rome 1724
- McCulloch H "Congenital Syphilis as a Cause of Heart Disease" *Am Heart J* 1930, VI 136
- Magill T P "Syphilitic Myocarditis" *Bull Johns Hopkins Hosp* 1935 LVII 27
- Maynard E P Jr "The Present Status of the Diagnosis of Uncomplicated Syphilitic Aortitis" *Bull New York Acad Med* 1942 XVIII 383
- Moore J E Dangle J H and Reisinger J C "Diagnosis of Syphilitic Aortitis Uncomplicated by Aortic Regurgitation or Aneurysm Comparison of Clinical and Necropsy Observations in One Hundred and Five Patients" *Arch Int Med* 1932, XLIX 753
- "Treatment of Cardiovascular Syphilis Results Obtained in Fifty three Patients with Aortic Aneurysm and in One Hundred and Twelve with Aortic Regurgitation." *Ibid* 1932 XLIX 879
- Morgagni G B *De Sedibus et Causis Morborum* Ex typog Remondiniana Venice 1761
- Nichols C F "A Study of Syphilis of the Aorta and Aortic Valve Area" *Ann Int Med* 1940 XIV 960
- Norris R F "Syphilitic Aortitis in Childhood and Youth Report of Two Cases with Sudden Death" *Bull Johns Hopkins Hosp* 1935 LVII 206
- Padget P and Moore J E "The Results of Treatment in Cardiovascular Syphilis A Report of Three Years Additional Observation" *Am Heart J* 1935 X 1017
- Pare A *Opera Chirurgica* Apud J Fischerum Francofurti and Moenum 1617 (French translation Paris 1840 Vol 1 p 372) (1st French ed 1664)
- Reifenstein E C "Acute Gummatous Myocarditis Simulating Acute Myocardial Infarction" *Ann Int Med* 1936 X 241
- Reuter K "Ueber Spirochaete pallida in der Aortenwand bei Heliöser Aortitis" *Munch med Wchnschr* 1906 LIII 778
- Seydel F C "Über die luetische Erkrankung der Herzkrankgefäße mit einem Fall eines syphilitischen Aneurysmas an dem vorderen absteigenden Ast der linken Kranzarterie" *Ztschr f Kreislauff* 1935 XXVII 265
- Stadler E *Syphilis des Herzens und der Gefäße* Theodor Steinkopff Dresden and Leipzig 1932
- Stone C T and Vanzant F R "Heart Disease as Seen in a Southern Clinic A Clinical Pathological Survey" *JAMA* 1927 LXXXIX 1473
- Venzoni M "La sifilide dell apparato circolatorio dal punto di vista anatomopatologico" *Arch Ital d anat e istol pat* 1939 X 171
- Warthin A S "Myxoma like Growths in the Heart Due to Localization of Spirochaete Pallida" *J Infect Dis* 1916 XIX 138
- "Sudden Death Due to Exacerbation of Latent Syphilitic Myocarditis" *Am Heart J* 1925 I 1
- Welty J W "Necropsy Survey of Cardiovascular Syphilis with Particular Reference to Its Decreasing Incidence" *Am J M Sc* 1939 CXCII 782
- White P D Chamberlain F L and Nelson S R "Rupture of Aorta into Pulmonary Artery with Long Survival" *Ann Int Med* 1941 XV 589
- White P D and Jones T D "Heart Disease and Disorders in New England" *Am Heart J* 1938 III 302

- White P D and Wise N B "The Early Diagnosis of Cardiovascular Syphilis" *New England J Med* 1937 CCXVII 938
- Williams A W "Heart Disease in the Native Population of Uganda" *East African M J* 1938 XV 279
- Wright, J H and Richardson O "Treponemata (Spirochaetae) in Syphilitic Aortitis. Five Cases One with Aneurism" *Boston M and S J* 1909 CLX, 539

## Recent References (1944-1950)

- Buch H. "Prognosis of Late Syphilitic Cardiovascular Lesions" *Acta med Scandinav* 1945 CXXII 529
- Clawson B J "Syphilitic Cardiac Deaths in over Fifty Thousand Autopsies" *Minnesota Med.* 1950 XXXIII 437
- Ederken, J Ford, W T Falk M S and Stokes J H "Penicillin Treatment of Patients with Cardiovascular Syphilis in Congestive Failure" *Circulation* 1950 I 1355
- Elkeles A "Calcification of Ascending Aorta as a Diagnostic Sign of Syphilitic Aortitis" *Proc Roy Soc Med* 1949 XLII 867
- Goldstein P "Spontaneous Rupture of Syphilitic Saccular Aneurysms of the Ascending Aorta into the Pericardial Cavity with Hemopericardium Report of Sudden Death in Twenty nine Cases" *Arch Int Med* 1949 LXXXIV 540
- Kossmann C E, and Flaum G "Penicillin in the Treatment of Cardiovascular Syphilis" *Mod Concepts Cardiovas Dis* 1948 XVII No 1
- Moore J E "Cardiovascular Syphilis Summary of Recent Information with Special Reference to Treatment with Penicillin" *Am J Syph* 1949 XXXIII 43
- Moore J E Farmer T W and Hoekenga M T "Penicillin and the Jarisch Herxheimer Reaction in Early Cardiovascular and Neurosyphilis" *Tr A Am Physicians* 1948 LXI 176
- Peabody E Reader G G Dotter C T and others "Angiocardiography in Diagnosis of Cardiovascular Syphilis" *Am J M Sc* 1950 CCXIX, 242
- Porter R R "Penicillin in Cardiovascular Syphilis" *Virginia M Monthly* 1948 LXXV 357
- Scharfman W B Wallach J B and Angrist A "Myocardial Infarction due to Syphilitic Coronary Ostial Stenosis" *Am Heart J* 1950 XL 603
- Thorner M C Carter R A and Griffith G C "Calcification as a Diagnostic Sign of Syphilitic Aortitis" *Am Heart J* 1949 XXXV III 641
- Tucker H A and Farmer T W "Penicillin in Cardiovascular Syphilis Early Reactions to Administration" *Arch Int Med* 1947 LXXX 322
- Webster B and Reader G G "The Effect of Antisyphilitic Treatment on the Microscopic Appearance of Syphilitic Aortitis" *Am J Syph* 1948 XXXII 19
- White P D "The Relative Incidence of the Etiologic Types of Heart Disease in New England Compared to That of 25 Years Ago An Analysis of 3000 Cases" In press 1951



---

## CHAPTER 17

---

# THE HEART IN DIPHTHERIA, SCARLET FEVER, AND TUBERCULOSIS AND IN OTHER BACTERIAL INFECTIONS, INFESTATIONS, AND VIRUS DISEASES

---

Although this chapter is steadily shrinking in importance in the overall picture of cardiovascular disease because of current improvement in the control of infectious diseases both prophylactically and therapeutically throughout the world our knowledge of the cardiovascular effects of many diseases has widened and deepened during the last generation as in the case of the virus diseases

Two or three generations ago the bulk of all heart disease was blamed on infections many cases were rightly so labeled but many more were incorrectly diagnosed particularly those with unrecognized congenital hypertensive and coronary heart disease Now infectious cardiovascular defects are known to comprise but a minority of all cases of clinical heart disease one reason for this change in viewpoint is the actual decrease in certain serious infections that can cause primary damage to the circulation but the more significant reason is the correction of the old time exaggerated point of view It is true however that many diseases which may be fatal show changes in the heart that are terminal in nature though not present in serious degree during life and that even the infections which do not directly cause heart disease can be serious or fatal complications in cardiac cases so that their control does have an important effect on the longevity of persons with heart disease An interesting comparison of the standardized death rates per 100 000 among insured persons aged 1 to 74 years in this country in the years 1917 1941 and 1948 has recently been made possible (*Statistical Bulletin* Metropolitan Life Insurance Company March 1942 Vol 23 No 3 Dublin personal communication 1949) diphtheria in 1917 showed a rate of 21.7 in 1941 only 0.7 and 0.4 in 1948 syphilis 19.1 in 1917 9.1 in 1941 and 4.8 in 1948 pneumonia (all forms) 131.8 in 1917 23.0 in 1941 and 15.2 in 1948 typhoid

fever 12.0 in 1917, 0.8 in 1941, and 0.1 in 1948 and tuberculosis (all forms) 202.2 in 1917, 40.9 in 1941 and 25.9 in 1948

Having considered in the last three chapters the more important cardiovascular infections, rheumatic acute and subacute bacterial and syphilitic we turn now to other infections which have a relatively uncommon or unimportant effect on the heart. Only occasionally do a few of these infections cause serious heart disease.

### DIPHTHERIA

Diphtheria during and following World War II has had a recrudescence of importance because of its increased frequency in the wake of the hardships in Europe and Asia and of its protean form among the military forces of the U.S.A. It often causes important damage to the heart muscle but happily it has been robbed of so much of its threat in recent years by large scale prevention of the disease in the first place and secondly when it does occur by the use of antitoxin that much less diphtheritic heart disease is nowadays diagnosed than was the rule a generation ago. During World War II nonfaucial diphtheria was on occasion unrecognized when it attacked other parts of the body especially the skin and serious cardiac effects were at times noted before a correct diagnosis was made.

**Pathology** The acute effect of severe diphtheria which is not quickly or sufficiently combated by antitoxin may be serious. There is clear evidence that grave myocardial damage may occur and that this may lead to death. The diphtheria bacillus itself is rarely encountered in the heart; it acts evidently through the toxin it produces which circulating in the blood stream reaches the heart muscle. The necrosis (Figure 90) produced in the myocardium may be found only at postmortem examination or it may give evidence during life by the production of various grades of atrioventricular or intraventricular block (shown by electrocardiogram) or rarely of heart failure. In some cases there may be multiple small hemorrhages throughout the heart as well as in other parts of the body (as in the liver and intestines) and it seems likely that such hemorrhages in the heart muscle may play some role in the sickest cases. Undoubtedly death during diphtheria results from the myocardial involvement in a considerable percentage of the fatal cases; such death may come abruptly without warning or after giving evidence such as that noted above. Endocarditis and pericarditis are not caused by diphtheria, except in unique cases (Sutherland and Willis 1936).

There is very infrequently any clinical evidence of a chronic effect on the heart from diphtheria even when it has been severe. Survival usually means escape from any permanent or serious heart disease. Slight lesions which may be discovered by microscopic examination of the myocardium doubtless occur in some cases but they are not demonstrable by clinical examination. Therefore it is reasonable to infer that any serious sequelae are absent rather than present. Rare cases of chronic atrioventricular or intraventricular heart block

# THE HEART IN DIPHTHERIA, SCARLET FEVER, AND TUBERCULOSIS AND IN OTHER BACTERIAL INFECTIONS, INFESTATIONS, AND VIRUS DISEASES

---

Although this chapter is steadily shrinking in importance in the overall picture of cardiovascular disease because of current improvement in the control of infectious diseases both prophylactically and therapeutically throughout the world our knowledge of the cardiovascular effects of many diseases has widened and deepened during the last generation as in the case of the virus diseases

Two or three generations ago the bulk of all heart disease was blamed on infections many cases were rightly so labeled but many more were incorrectly diagnosed particularly those with unrecognized congenital hypertensive and coronary heart disease Now infectious cardiovascular defects are known to comprise but a minority of all cases of clinical heart disease one reason for this change in viewpoint is the actual decrease in certain serious infections that can cause primary damage to the circulation but the more significant reason is the correction of the old time exaggerated point of view It is true however that many diseases which may be fatal show changes in the heart that are terminal in nature though not present in serious degree during life and that even the infections which do not directly cause heart disease can be serious or fatal complications in cardiac cases so that their control does have an important effect on the longevity of persons with heart disease An interesting comparison of the standardized death rates per 100 000 among insured persons aged 1 to 74 years in this country in the years 1917 1941, and 1948 has recently been made possible (*Statistical Bulletin* Metropolitan Life Insurance Company March 1942 Vol 23 No 3 Dublin personal communication, 1949) diphtheria in 1917 showed a rate of 21.7, in 1941 only 0.7 and 0.4 in 1948 syphilis 19.1 in 1917 9.1 in 1941 and 4.8 in 1948 pneumonia (all forms) 131.8 in 1917 23.0 in 1941 and 15.2 in 1948 typhoid

but weakness and listlessness are the commonest symptoms accompanying the cardiac involvement and these may be due rather to the general effect of diphtheria on the whole body (nervous system vasomotor control and musculature) than to the cardiac involvement. With the rare complication of congestive heart failure cough may appear.

**Signs** Signs also are relatively infrequent. There may appear pallor, cyanosis, cardiac enlargement due to dilatation, tachycardia, diastolic gallop rhythm (which may be due either to delayed atrioventricular conduction or to cardiac dilatation and failure or to both), an apical systolic murmur due to secondary mitral regurgitation or an arrhythmia which may include an ominous ventricular paroxysmal tachycardia and rarely bradycardia due to heart block. There may be hepatic engorgement and tenderness and pulmonary rales due to heart failure. If a majority of these signs are present the immediate prognosis is very serious.

Fever is not a sign of diphtheritic myocardial involvement; in fact the most serious heart trouble exists after the fever of the acute illness is over. Fluoroscopic examination if such can be safely undertaken may show dilatation of the heart. Electrocardiographic examination is of greater value than any other special method by revealing the degree of atrioventricular or intraventricular (bundle branch) block or more commonly abnormalities of the T wave. Blood and urine examinations and other such studies are not of much help.

**Course and prognosis** When involvement of the heart in diphtheria reveals itself by signs or symptoms the course of the illness is short and fatal or long and exhausting with the prognosis in doubt. Although about half of such cases recover they are not out of danger for weeks and they may die suddenly at any time during this period of convalescence. Heart block is usually a fatal sign especially bundle branch block. A follow up study of cases of diphtheria at the South Department of the Boston City Hospital has revealed a few survivors after the development of atrioventricular or intraventricular block. On recovery from the diphtheria such cases have lost all electrocardiographic evidence of heart block except for very rare individuals who retained some degree of atrioventricular block; there were none in this particular series in whom intraventricular (bundle branch) block persisted (Faulkner and Place, personal communication) though one such case was reported by Perry (1939). T wave changes also tend to clear up although rarely inversion of this wave in Lead 1 or Lead 2 has persisted for a few months or even a few years.

**Complications** Heart block and cardiac dilatation have been mentioned as grave cardiovascular complications of diphtheria. There are two other serious cardiovascular complications difficult to analyze, namely vagal and splanchnic paralyses. The tachycardia in diphtheria has sometimes been ascribed to vagal paralysis resulting from damage to this nerve by the diphtheritic toxin and also to circulatory failure from vasomotor (splanchnic) paralysis; the latter has also been blamed for some of the deaths. It seems

probable that these are real factors how responsible they may be as compared to actual myocarditis we do not know, it is probable that all these factors operate simultaneously in a seriously sick patient

**Treatment** In the first place adequate antitoxin should be given at the onset of the diphtheria, the more severe the illness the more units of antitoxin should be administered even up to 50,000 or 100 000 This early therapy is the most important of all measures to protect the heart Rest in bed should be enforced for at least several days after all signs of infection have gone even in the mildest cases and for several weeks in the severe cases especially if there have been symptoms or signs of cardiac involvement For serious cardiovascular complications absolute rest and intravenous dextrose (glucose) injections (25 to 100 cc of 50 per cent solution daily or oftener) have been found more helpful than other measures Digitalis, epinephrine (adrenaline) and other stimulating drugs with the possible exception of caffeine and theophylline ethylene diamine (aminophyllin), have been disappointingly ineffective in the treatment of cardiac failure and vasomotor collapse in diphtheria early adequate treatment of the infection itself will prevent such complications

**Differential diagnosis** The differential diagnosis of diphtheritic heart disease is usually not difficult It must be distinguished from the unimportant neuro-circulatory asthenia (effort syndrome) that may come in diphtheria as in any infectious disease from the tachycardia due to vagal paralysis and from coincident heart disease such as rheumatic valvular disease It must be borne in mind also that diphtheria of the skin or mucous membranes other than of the fauces can result in serious heart disease

## SCARLET FEVER

There is strictly speaking probably no such entity as the scarlet fever heart although there may occasionally occur temporary toxic cardiac effect Permanent heart disease certainly does however follow scarlet fever in rather rare cases Evidence that has been accumulating in the past few years indicates that scarlet fever like certain other streptococcus infections merely plays the role of an activating agent of the rheumatic infection in the heart in individuals who belong to rheumatic families (Paul Sahinger and Zuger 1934 Faulkner Place and Ohler 1935) Further important evidence that scarlet fever per se does not cause any important myocardial disease has been advanced by Shookhoff and Taran (1931) who found in the electrocardiograms of fifty consecutive patients with scarlet fever only minor changes in the T waves or Q T intervals in 10 per cent and no prolongation of the P R interval in any case in contrast to the frequent changes especially prolongation of the P R interval in acute rheumatic heart disease The statistical evidence which we possess at present indicates that not over 0.5 per cent of all cases of scarlet fever are complicated by endocarditis or pericarditis or both and that a very small fraction of 1 per cent of cases of heart disease originate during scarlet fever The chronic valvular disease that results is of rheumatic type

but it does not ordinarily develop to the stage of marked valve deformity. The mitral is the valve ordinarily attacked, the aortic rarely. In a series of 602 cases of scarlet fever observed during one year (August 1943 to August 1944) 36 (6 per cent) showed cardiac complications during the acute illness. 32 with myocarditis, of whom one died with atrial fibrillation and two others showed partial a v block, and 4 with endocarditis (Neubauer 1945).

It is especially in patients in whom acute polyarthritis complicates scarlet fever that acute cardiac infection tends to occur. valvular disease has, however, also been reported in scarlet fever with no arthritis. It is important always to wait until the completion of convalescence before ascribing to valvular damage an apical systolic murmur which may be merely a temporary accompaniment of the scarlet fever itself. More than half of the cases of acute endocarditis or pericarditis occurring in scarlet fever show an arthritis at the onset of the heart disease.

The pathologic changes are similar to those of rheumatic heart disease both in the acute and in the chronic stages.

There are no symptoms of the heart involvement itself except for a slight prolongation of the fever and occasionally pain from pericarditis.

The only signs are the development of slight cardiac enlargement and of heart murmurs, rarely the occurrence of a pericardial friction rub during or at the end of the scarlet fever and minor electrocardiographic changes noted above.

The treatment of scarlet fever, and therefore favoring the prevention of the infrequent heart disease that results, has been improved since the introduction of penicillin which should be administered at the very onset of the hemolytic streptococcus sore throat which ushers in the scarlet fever, and continued until convalescence begins, in order to prevent especially the formerly serious and common complication of mastoiditis.

The differential diagnosis is inconsequential in that the acute heart disease with or without pericarditis occurring during scarlet fever and the chronic valvular disease that may follow are indistinguishable from rheumatic heart disease, acute and chronic.

#### STREPTOCOCCUS HEMOLYTICUS INFECTION WITH HEMORRHAGIC NEPHRITIS

Among others Whitehill, Loncope and Williams (1939) have called attention to this serious disease in childhood which is not infrequently attended by a complication of cardiac dilatation and even heart failure early in the illness (71 per cent of the series of 138 cases of Whitehill et al.) but fortunately nowadays penicillin given as near the onset of the disease as possible can result in much improvement and may help to prevent the more serious cardiac effects provided the streptococcus infection itself is still active, the penicillin does not cure the nephritis itself. The death rate used to be fairly high (20.3 per cent of the 59 severe cases in the series just mentioned) recovery was

slow but the heart did often return to normal (see also Chapter 23) Happily the picture has changed and this disease should be on the way out

### PNEUMONIA

Pneumonia either lobar or bronchial in type may prove a great strain for an already weakened or diseased heart but it does not itself cause serious heart disease except in rare instances when acute bacterial (generally pneumococcus) endocarditis or a septic pericarditis occurs in either case almost always a fatal complication in the days before chemotherapy with the sulfonamide drugs and the introduction of the antibiotics especially penicillin but this complication is now largely preventable and most cases that do occur are curable by the use of these drugs (formerly sulfadiazine sulfathiazole or sulfapyridine 1 to 2 gm 15 to 30 gr 3 or 4 times a day for a few days under careful observation and with blood titration and now preferably procaine penicillin by intramuscular injection 300 000 units daily for a few days to a week or terramycin (chloromycetin, or aureomycin by mouth about 500 mg every 6 hours for a week) The various antibiotics should be appraised as to their efficacy by direct testing on the growth of the responsible organisms themselves

Electrocardiograms in the course of and immediately following severe pneumonia may show various arrhythmias and sometimes important changes such as inversion of the *T* waves and prolongation of the *PR* interval the more severe the disease the more marked the changes but these abnormalities subside during convalescence Undoubtedly they are to be ascribed to a direct toxic effect on the myocardium (Cohn and Jamieson 1917 Master et al 1931) At postmortem examination the heart muscle cells may show cloudy swelling but such a finding does not constitute real heart disease

As will be observed concerning typhoid fever and exanthematic typhus the weakness and collapse due to pneumonia are not the result of cardiac failure but of the infection It is therefore not to be expected that routine digitalis therapy in pneumonia should help except when there is obvious congestive failure or a rare complication such as atrial fibrillation or atrial flutter

### TYPHOID FEVER

The rare invasion of the endocardium by the typhoid bacillus producing acute or subacute bacterial endocarditis has already been mentioned (Chapter 15) Much more common but of little or no clinical importance is the finding at postmortem examination of slight to moderate scattered toxic changes of muscle fibers and interstitial tissue consisting of cloudy swelling and infiltration with small round cells in the majority of cases dying of typhoid fever Also periarteritis and endarteritis have been found in the blood vessels of such patients even to the extent of causing ulceration and aneurysm of the aorta Pericarditis is a rare complication

Generally the heart is not affected to any important or appreciable degree

in typhoid fever. Not infrequently, however, *T* wave changes (flattening or inversion) and rarely delayed atrioventricular conduction can be found by electrocardiogram during the acute infection but no high degree of block (Brow 1929 Porter and Bloom 1935 Mainzer 1947) and if cardiovascular symptoms occur they are in the nature of the effort syndrome usually found in infectious disease. Of course organic heart disease of other nature may happen to complicate and be overburdened by the infection but it is wrong to treat the heart with digitalis or other such drug in order to combat the symptoms of effort syndrome or of circulatory failure due to vasomotor paresis. It is apparently not heart failure that kills in typhoid fever but the toxic effect with weakness and vascular collapse resulting from the infection. Also avitaminosis associated with the malnutrition during a prolonged illness with typhoid fever may play a role electrocardiographically and otherwise (Rachmilewitz and Braun 1948).

### TUBERCULOSIS

Tuberculosis does not cause heart disease itself except in rare cases in which there is direct tuberculous invasion of the myocardium or endocardium. Pericardial tuberculosis is however occasionally encountered as either (1) an isolated lesion (2) a part of a polyserositis or (3) an extension from mediastinal tuberculosis.

Tuberculosis of the myocardium is infrequently found at postmortem examination as a part of a miliary tuberculous process or in the form of a solitary tubercle or abscess. It is an autopsy finding rarely even suspected during life. The miliary tubercles in the heart muscle almost never produce any symptoms or signs the illness being that usually observed in miliary tuberculosis. If invasion or pressure directly involves the atrioventricular conduction system heart block may occur with arrhythmia and slow pulse or myocardial tuberculosis may even cause congestive heart failure (Wilbur 1938 also personal observation 1947). Still more rare than disease of the heart muscle in miliary tuberculosis is a myocardial invasion by a solitary tubercle or tuberculous (cold) abscess such invasion is usually symptomless and without signs but it is capable of causing an aneurysm of the heart wall which may even lead to rupture and to death. In a series of 7 683 cases of tuberculosis myocardial tuberculosis was found 49 times (0.63 per cent) (Raviart 1906).

Tuberculous endocarditis is also rare infrequent cases usually of miliary tuberculosis revealing at autopsy tubercles in the endocardium of the heart walls and of the valves or tuberculous ulceration of the endocardium. Tubercle bacilli have been found in such endocardial lesions. There is no evidence that chronic valvular disease can originate either directly from tuberculous inflammation or indirectly from the toxic effect of tuberculosis elsewhere in the body.

Tuberculous pericarditis is not rare. It is an important type of acute and also of chronic pericardial disease isolated or more commonly associated



with a similar involvement of pleura or with a tuberculous involvement of the mediastinum arising from lymphatic glands, spinal caries, or other cause. It is not usually accompanied by myocardial or endocardial tuberculosis but in rare cases for example in miliary tuberculosis it may be thus complicated. Isolated tuberculosis of the pericardium unsuspected during life has been discovered to be an occasional cause of death in elderly individuals (Thompson 1933).

Pericardial effusion is a common accompaniment of pericardial tuberculosis and may be very slow and insidious in its onset causing few or no symptoms at first but finally incapacitating the patient by its pressure effect, which prevents adequate filling of the heart (cardiac tamponade—see Chapter 27) or by associated fever and weakness. The effusion often in fact usually hemorrhagic in character may develop to enormous size (even up to 2 or 3 liters) and because of its very gradual growth may be astonishingly well supported for a long time even for many weeks. It is much better endured by the patient than is the more acute rheumatic pericardial effusion of the same amount of fluid. The tuberculous effusion may be spontaneously absorbed or with the development of serious symptoms and signs require paracentesis. The symptoms—dyspnea, cough and oppression—come from pressure effects and but rarely include sharp pains such as are frequent in rheumatic pericarditis. The signs are those of a small, moderate or large accumulation of fluid in the pericardium with slight, moderate or enormous increase of the area of percussion dullness over the heart and of the roentgen ray shadow. With a large effusion the arterial blood pressure is low, especially the pulse pressure, there is often a well marked paradoxical pulse and the systemic venous pressure is elevated with resulting prominence of the jugular veins and pulse and enlargement of the liver: these are signs of acute or subacute constrictive pericarditis (the so called cardiac tamponade). A pericardial friction rub may be heard over the precordium even in the presence of a large effusion.

After the subsidence of the acute process a serious chronic pericarditis may develop frequently with involvement of the mediastinum. If extensive this chronic mediastinopericarditis may so cramp the heart chambers and great veins that the entrance of blood into the heart is obstructed. Generally the obstruction is most manifest in the hepatic veins with resulting hepatic engorgement and ascites: this condition has therefore been called chronic mediastinopericarditic pseudocirrhosis of the liver or Pick's disease (Chevers 1842, Pick 1896) but a better designation is chronic constrictive pericarditis (see Chapter 27). Sometimes the process may be slight without handicap from the nonconstricting or only slightly constricting pericardial adhesions.

Tuberculosis of the blood vessels may occur in rare instances causing endarteritis, granulomata and even aneurysmal dilatations. The invasion may be either from the blood stream or from infected tissue (lymph nodes for example) contiguous to aorta or other blood vessel.

The introduction of streptomycin has given promise of aid in a few instances of tuberculous pericarditis: this drug in the dosage of 2 to 4 gm daily

has been apparently helpful but its toxic effects are a distinct drawback (see page 403 in Chapter 15)

The relationship of heart disease to tuberculosis of the lungs It has long been said that pulmonary tuberculosis is rare if there is considerable mitral stenosis This appears to be true the reason is not clear but it may be that the chronic pulmonary congestion resulting from mitral stenosis makes it difficult for the tubercle bacillus to gain a foothold In one series of 300 cases of mitral stenosis there was found but one case of pulmonary tuberculosis (0.3 per cent) and in a series of 20 000 cases of pulmonary tuberculosis there was reported to be but one case of mitral stenosis (0.005 per cent) (Monte negro 1919) Valvular heart disease of other sort (not marked mitral stenosis) is however occasionally and incidentally seen in pulmonary tuberculosis the combination was reported in 29 out of 1 097 cases of pulmonary tuberculosis valvular heart disease or both examined post mortem (Calthrop 1920) in 31 out of a series of 13 000 cases of pulmonary tuberculosis (Kellner 1921) and in 0.9 per cent of 7 115 necropsies on tuberculous patients (Brown quoted by Hawes 1932) An analysis of 522 adults with pulmonary tuberculosis revealed 3 cases of rheumatic heart disease and 2 of congenital heart disease (Buckingham and Hoffman 1935)

In contrast to the rarity of pulmonary tuberculosis in cases of pronounced mitral stenosis it is said to be rather a usual development in congenital stenosis of the pulmonary orifice (Austrian 1933) In this regard it is of interest that just the opposite conditions exist in the pulmonary circulation with these two lesions in mitral stenosis the pulmonary circulation is engorged and in pulmonary stenosis it is depleted

Much more important than the possible protective action of mitral stenosis in the case of phthisis is in rare cases the deleterious effect of extensive pulmonary tuberculosis on the heart This is not the production of the familiar so-called drop or vertical (or atrophied) heart which is sometimes seen in the more slender victims of tuberculosis with low diaphragm and general atonic state such a drop heart is of little or no importance in itself Rather is it the strain on the right ventricle resulting from increased pressure produced in the pulmonary circulation by obstruction caused by extensive destruction of pulmonary tissue fibrosis and pleural adhesions This strain may eventually in a few cases produce some right ventricular enlargement rarely to a considerable degree and not marked enough to cause definite increase beyond the normal in the percussion or roentgen ray size of the heart so that the change may easily escape notice In a very few cases actual failure of the right ventricle may occur but this is much rarer than in the case of chronic pulmonary fibrosis and emphysema of other cause which will be discussed in Chapter 20 During life there may be a great variety of size and shape of the heart shadow in the presence of active pulmonary tuberculosis (Porter and Gordon 1937)

Finally it is to be recognized that in patients with active tuberculosis in the lungs or elsewhere there is commonly as in the case of other infections

a certain degree of neurocirculatory asthenia with dyspnea palpitation and heartache which may on hasty analysis be wrongly ascribed to heart disease or to a toxic effect of tuberculosis of the heart

The course prognosis and treatment of tuberculosis of the heart and pericardium resolve themselves primarily into those of the underlying tuberculosis be it miliary pulmonary or of the nature of polyserositis The prognosis is always grave though some cases recover this number has increased somewhat since the introduction of streptomycin A pericardial effusion may need to be tapped and cases of chronic constrictive pericarditis may require surgical relief by pericardial resection Active tuberculosis of pericardium and heart must be treated by rest and good nursing care and a trial of streptomycin just as in the case of active pulmonary tuberculosis but the prognosis is always serious

### EPIDEMIC CEREBROSPINAL MENINGITIS

Meningococcus infection may in rare cases involve the heart and cause an acute bacterial endocarditis or pericarditis as noted in Chapter 15 but such cardiac involvement is now largely preventable or amenable to recovery by the use of chemotherapy Meningococcic myocarditis has also been reported (Saphir 1936)

### GONORRHEAL INFECTION

Acute or chronic gonorrhea may in rare cases infect the heart especially following gonorrheal arthritis or a virulent illness of other nature due to the same organism The involvement occurs in the form either of acute or of subacute bacterial endocarditis and is no longer as it once was fatal the newer chemotherapy being a specific remedy in most cases

### OTHER BACTERIAL DISEASES INCLUDING SEPTIC INFECTIONS

Erysipelas septic infections and pyemia due to streptococcus or staphylococcus used to be occasional causes of acute bacterial endocarditis septic (purulent) pericarditis and myocardial abscesses Generally these were but terminal manifestations and were not responsible for death but sometimes they constituted the chief or most important part of the disease Treatment used to be of little avail when the heart itself was diseased but both prevention and recovery of cardiac and pericardial complications now may follow the use of the antibiotics (especially penicillin) and of the sulfonamide drugs aided by pericardiotomy and drainage in the case of purulent pericarditis

### RICKETTSIAL DISEASES

Typhus fever Myocardial lesions and vascular disease (endarteritis) may result from exanthematic typhus fortunately now rare in civilized countries at peace they are as a rule of little or no significance Transient T wave ab-

normalities in the electrocardiogram are common during the acute infection (Norvut 1947). Complete arterial obstruction and gangrene may however complicate a few cases. The toxicity and vasomotor paralysis resulting from this infection may kill but involvement of the heart is probably not responsible for death. Endocarditis and pericarditis do not occur except from a secondary infection.

Another important rickettsial disease which has been found even more constantly to be associated with myocardial involvement namely *tsutsugamushi* fever or scrub typhus was studied during World War II. A large proportion of electrocardiograms of cases of scrub typhus has shown abnormalities chiefly in the T waves with recovery in most cases.

Rocky Mountain spotted fever also falls into the group of rickettsial diseases and may affect the myocardium during the acute illness.

### VIRUS DISEASES

An interesting and important advance in our knowledge of the effect of infections on the heart has taken place during recent years in the field of the virus diseases. In most instances the victims of such infections escape any serious cardiac injury but in a certain number of instances rare as a rule the myocardium may be seriously affected. Virus pericarditis has also of late been identified.

Influenza had long been suspected and by some so incriminated but only in the last few years has actual proof been presented (Finland et al. 1945). It is quite possible that lesser lesions of the heart muscle have often resulted from influenza but serious or fatal myocarditis is rare. Most of the symptoms which years ago were attributed to such a condition were characteristically those of a fatigued state or neurocirculatory asthenia which so often complicates the convalescence from any infection (see Chapter 22).

Mumps has been shown to produce temporary atrioventricular block in rare cases clearing with convalescence (Rosenberg 1945).

German measles (rubella) has been shown to have in many instances a serious effect on the eyes and heart of a fetus if it attacks the mother during the first three months of pregnancy (Gregg 1941 Swan 1943).

Yellow fever may give rise to nonspecific myocardial inflammation and degeneration in fatal cases (Cannell 1928).

*Poliomyelitis*. Recently myocardial changes characterized by perivascular infiltration of lymphocytes and neutrophils have been reported in 6 out of 7 cases with poliomyelitis who died suddenly during the acute or convalescent stages (Saphir and Wile 1942) and several other observers have confirmed these findings since (Geffer et al. 1947 Ludden and Edwards 1948).

*Infectious hepatitis* and *infectious mononucleosis* have also been found to cause in some cases myocardial involvement as indicated electrocardiographically.

Still other viruses need further appraisal in this respect.

## TRICHINIASIS

It was long known that trichiniasis may involve the myocardium as well as other muscles in the body but the possible frequency with which the trichinae invade the heart in well infested cases was not pointed out until 1935 (Spink 1935). A serious effect directly from this heart involvement itself has not been found but changes in the electrocardiogram (flattening or inversion of the T waves, low voltage of QRS waves and intraventricular block) in some cases (6 of 18 patients with myocardial trichiniasis in Spink's series) may justifiably be attributed to the presence of the parasites in the heart muscle. In another series of 44 cases of trichiniasis of mild type however only 2 showed possible clinical evidence of myocardial involvement (Beecher and Amidon 1938). There is no specific therapy.

## TRYPANOSOMIASIS

A cause of heart disease in South America (especially in Brazil) rare or nonexistent elsewhere namely cardiac trypanosomiasis has been frequently reported in recent years following its discovery in human beings by Chagas in 1909. This consists of the invasion of the myocardium in childhood by trypanosomes (Figure 91, illustration below) with foci of inflammatory reaction which later lead to cardiac weakness and failure and arrhythmias in

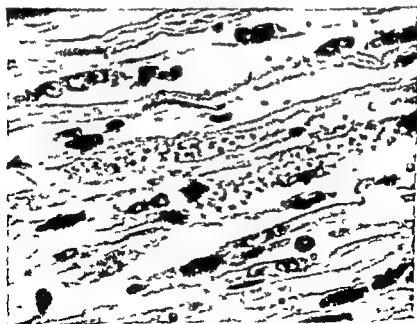


FIG. 91 Microphotograph showing myocardial trypanosomiasis (Chagas disease). Note *Trypanosoma cruzi* near the center of the field (kindness of Drs. C. Chagas and E. Menezes, Brazil and Frank Wilson, Ann Arbor, Michigan).

middle life Sudden death may result The pericardium endocardium and valves are not involved but the myocardium is said to be more often involved than in any other disease In the chronic cases multiple areas of fibrosis may be found scattered through the heart muscle Thousands of cases of this remarkable type of heart disease have been seen in Brazil but it has not yet been encountered in the United States or Europe

### ECHINOCOCCUS DISEASE

Infection with the echinococcus may involve the heart and a number of cases of hydatid cysts in or attached to the walls of atria and of ventricles or interventricular septum have been reported It is usually but a part of general echinococcus disease I have encountered such cases in Greece (1948)

### ACTINOMYCOSIS

Actinomycosis of heart and pericardium is a very rare infection Thirty years ago the case of a man 34 years old was reported with initial lesion in the esophagus and secondary invasion of the heart pericardium lung and pleura it was noted that twenty two other cases had been described previously (Letulle and Hufnagel 1919)

### INTESTINAL PARASITES

Most of the parasites that invade the intestinal tract of man do not affect the heart these include the roundworm (ascaris) the pinworm (oxyuris) and the ordinary tapeworms (taenia saginata and taenia solium) but the hook worm (ankylostoma) and less commonly the fish tapeworm (dibothriocephalus latus) may by their production of severe anemia cause an important degree of cardiac dilatation and loud murmurs (see Chapter 23)

### OTHER INFECTIONS AND INFESTATIONS

A few other diseases may involve the heart for example *Brucella melitensis* (Malta fever) sarcosporidial infection of the myocardium filariasis (with ova found in the heart) strongyloidiasis cardiac heterophyidiasis (infestation with flukes from raw fish) and cysticercosis of the myocardium (and brain) In the sixteenth century there were frequent reports of worms in the chambers of the human heart before the days when it was recognized that these supposed worms were actually elongated blood clots both ante mortem and post mortem it is however true that the dog's heart may contain worms (*Dirofilaria immitis* see Query JAMA 1924 CIII 1728) which introduced by insect bite go through a cycle of development and then migrate in adult life along the veins into the right heart chambers where by their accumulation en masse the individual thread like filaria attaining the length of one to two feet, may actually block the circulation and cause pulmonary embolism Rheumatoid arthritis periarthritis nodosa and conditions like lupus erythe-

matosis allied to these are quite frequently attended by heart disease but it is still difficult or impossible in view of our ignorance as to their etiology to label them as infections or even reactions to infections or toxic states (see Chapter 23)

### FOCAL INFECTIONS

Focal infections may have a deleterious effect on the heart either directly or indirectly. Actual cardiac disease of the nature of bacterial endocarditis is known to follow an acute focal infection like that of tonsil of middle ear or of skin. But this happens only rarely except in the case of dental infections and extractions which almost certainly are a very important source of entry of the *Streptococcus viridans* into the body to inaugurate the grave infection of subacute bacterial endocarditis in cases of rheumatic or congenital heart disease (see Chapter 15). It behooves us in such cases to use the greatest vigilance in avoiding strain from too much operative work at any one time and in combating the serious results of dental and other focal infections by the use of the antibiotics (in particular penicillin) and of the sulfonamide drugs and otherwise.

How frequently slight myocardial damage or a mild endocardial lesion with recovery may occur with such focal infections we do not know but there exists no proof that this is even an occasional happening. We do know that heart disease already existing is sometimes aggravated by the presence of focal infections with the appearance of arrhythmia or of symptoms of congestive failure or angina pectoris or with their increase if already present. Whether or not there is actual heart disease cardiac arrhythmia may be set off or aggravated by focal infections such arrhythmia is as a rule entirely unimportant in itself consisting of premature beats (extrasystoles) or paroxysms of tachycardia but sometimes it may comprise atrial fibrillation or flutter or prolonged paroxysmal tachycardia. Among the focal infections which may precipitate or aggravate cardiac arrhythmia congestive failure or angina pectoris are chronic cholecystitis prostatitis pyelitis colitis infection of gums apical tooth abscesses frontal sinusitis lung abscesses and other similar troubles.

Correction of these focal infections by surgery or by other measures (if the circulatory condition permits) may relieve the patient of his temporary state of ill health or at least cause improvement. The risk of such corrective procedures is usually justified provided too much is not attempted at one time (the removal of more than one or two infected teeth at one sitting for example, may result in vasomotor shock or may itself precipitate heart failure and death). The wisest course then is to view focal infections so far as the heart is concerned neither with overmuch fear nor with excessive disregard to consider them as possible important factors producing a state of ill health which may cause strain on the heart and to eradicate them if possible and feasible. However it is a mistake to perform an operation of choice and not of necessity for example to remove a symptomless gallstone (or to correct surgically a

simple inguinal hernia) in the face of severe angina pectoris or of congestive failure

### INFECTIONS NOT CAUSING HEART DISEASE

Many infections never cause heart disease although they may precipitate such trouble as failure or atrial fibrillation in hearts already diseased or they may be attended by complicating infections which do cause heart disease. This is particularly true of most of the contagious diseases of childhood: whooping cough (pertussis), chickenpox (varicella) and measles (rubeola). The acute respiratory tract infections—rhinitis, sinusitis, pharyngitis, laryngitis, tracheitis and bronchitis—do not of themselves cause heart disease, but like tonsillitis they may occasionally precipitate the rheumatic infection which does almost always damage the heart. The same statement is true of otitis media, but infections of the gastrointestinal and genitourinary tracts very rarely precipitate any heart trouble.

### BIBLIOGRAPHY

#### DIPHTHERIA SCARLET FEVER TUBERCULOSIS OTHER INFECTIONS AND INFESTATIONS

##### Diphtheria

- Alstead S "The Heart After Diphtheria" *Lancet* 1933 I 413  
 Engle M A "Recovery from Complete Heart Block in Diphtheria" *Pediatrics* 1949 III 772  
 Gore I "Myocardial Changes in Fatal Diphtheria: Summary of Observations in 221 Cases" *Am J M Sc* 1948 CCXV 257  
 Hume W E and Clegg S J "A Clinical and Pathological Study of the Heart in Diphtheria" *Quart J Med* 1914 VIII 1  
 Jones T D and White P D "The Heart After Severe Diphtheria" *Am Heart J* 1927 III 190  
 Kay C F and Livingood C S "Myocardial Complications of Cutaneous Diphtheria" *Bull US Army M Dept* 1945 IV 46  
 Metropolitan Life Insurance Co "Health Contrast World Wars I and II" *Statist Bull* 1942 XVIII No 3  
 Perry C H "Persistent Conduction Defects Following Diphtheria" *Brit M J* 1939 I 117  
 Sutherland J, and Willis R A "Endocarditis Due to Diphtheroid Bacillus Structurally and Culturally Resembling Diphtheria Bacillus" *J Path & Bact* 1936 XLIII 127  
 Thompson W P, Golden S E and White P D "The Heart Fifteen to Twenty Years After Severe Diphtheria" *Am Heart J* 1937 XIII 534  
 Warthin A S "The Myocardial Lesions of Diphtheria" *J Infect Dis* 1924 XXXV 32

##### Scarlet Fever

- Faulkner J M, Place E H and Ohler W R "The Effect of Scarlet Fever on the Heart" *Am J M Sc* 1935 CLXXXIX 352  
 Neubauer C "Cardiac Complications in Scarlet Fever" *Arch Dis Child* 1945 XX 81  
 Paul J, Salinger R and Zuger B "The Relation of Rheumatic Fever to Post scarlatinal Arthritis and Postscarlatinal Heart Disease—A Familial Study" *J Clin Investigation* 1934 XIII 503



Shookhoff C and Taran L M "Electrocardiographic Studies in Infectious Diseases II Scarlet Fever" *Am J Dis Child* 1931 XLII 554

### Pneumonia

- Cohn A E and Jamieson R A "The Action of Digitalis in Pneumonia" *J Exper Med* 1917 XXV 65  
 Master A M Romanoff A and Jaffe H "Electrocardiographic Changes in Pneumonia" *Am Heart J* 1931 VI 696  
 Saphir O and Amromin G D "Myocarditis in Instances of Pneumonia" *Ann Int Med* 1948 XXVIII 963

### Typhoid Fever

- Brow G H "The Heart in Typhoid Fever" *Canad M A J* 1929 XX 606  
 Mainzer F "Electrocardiographic Study of Typhoid Myocarditis" *Brit Heart J* 1947 IX 145  
 Porter W B and Bloom N "The Heart in Typhoid Fever A Clinical Study of Thirty Patients" *Am Heart J* 1935 X 793  
 Rachmilewitz M and Braun A "Electrocardiographic Changes in Typhoid Fever and Their Reversibility Following Niacin Treatment" *Am Heart J* 1948 XXXVI 284  
 Storti E Bobba P and Curti P C *Il Cuore nel Tifo Addominale* Typographia del Libro Pavia 1948

### Tuberculosis

- Anders J M "Tuberculosis of the Myocardium" *JAMA* 1902 XXXIX 1081  
 Andrews G W S Pickering G W and Sellors T H "The Aetiology of Constrictive Pericarditis with Special Reference to Tuberculous Pericarditis Together with a Note on Polyserositis" *Quart J Med* 1948 XVII 291  
 Austrian C R "Heart Disease and Its Relation to Tuberculosis" *Mod Concepts Cardiovas Dis* 1933 II No 3  
 Baker R D "Endocardial Tuberculosis" *Arch Path* 1935 XIX, 611  
 Buckingham W W and Hoffman J S "Pulmonary Tuberculosis Associated with Valvular Heart Lesions" *Missouri State M A J* 1935 XXXII 418  
 Calthrop G T "The Relation Between Valvular Disease of the Heart and Pulmonary Tuberculosis" *Tubercle* London 1920 I 263  
 Chevers N "Observations on the Diseases of the Orifice and Valves of the Aorta" *Guys Hosp Rep* 1842 VII 387  
 Hawes J H "The Heart in Pulmonary Tuberculosis" *New England J Med* 193 CCVII 874  
 Horn H and Saphir D "Involvement of Myocardium in Tuberculosis Review of Literature and Report of Three Cases" *Am Rev Tuberc* 1935 XXXII 492  
 Kellner F "Herzklappenfehler und Lungentuberkulose" *Ztschr f Tuberkulose* 1911 XXXV 33  
 Menon T B and Prasada Rao C A "Tuberculosis of the Myocardium Causing Complete Heart Block" *Am J Path* 1945 XXI 1193  
 Montenegro J V "Mitral Stenosis and Pulmonary Tuberculosis" *Arch espan d fisiologia* Barcelona 1919 I 89  
 Pick F "Ueber chronische unter dem Bilde der Lebercirrhose verlaufende Pericarditis (pericarditische Pseudolebercirrhose) nebst Bemerkungen über die Zuckergussleber (Curschmann)" *Ztschr f klin Med* 1896 XXIX 385  
 Porter R E and Gordon W H "Size of the Heart in Pulmonary Tuberculosis" *Am Rev Tuberc* 1937 XXXVI 82  
 Raviart H "La tuberculose du myocarde" *Arch d méd expér* 1906 XVIII 141  
 Schnitzer R "Myocardial Tuberculosis with Paroxysmal Ventricular Tachycardia" *Brit Heart J* 1947 IX 217  
 Thompson W P "Primary Tuberculosis of the Pericardium" *JAMA* 1933 C, 64-  
 Wilbur E L "Myocardial Tuberculosis Cause of Congestive Heart Failure" *Am Rev Tuberc* 1938 XXXVIII 769

## Other Bacterial Infections

- Bien C W and Tung C L. Electrocardiographic Changes in Cholera. *Chinese M J* 1933 XLVII 662
- Call J D Baggenstoss A H and Merritt W A "Endocarditis Due to *Brucella*. Report of 2 Cases. *Am J Clin Path* 1944 XIV 508
- Firestone G M. Meningococcus Endocarditis. *Am J M Sc* 1946 CCXI 556
- Saphir O. Meningococcal Myocarditis. *Am J Path* 1936 XII 677
- Whitehill M R Longcope W T and Williams R "The Occurrence and Significance of Myocardial Failure in Acute Hemorrhagic Nephritis. *Bull Johns Hopkins Hosp* 1939 LXIV 83

## Rickettsial Diseases

- Gubergitz M M. Zur Klinik der Herzstörungen als Folge des Fleckfiebers. *Klin Wchnschr* 1926 V 845
- Hälonen P I "Über die Veränderungen im Elektrokardiogramm und im Herzmuskel bei Epidemischem Flecktyphus. *Acta soc med Fennicae Duodecim* 1945 XXXIV 90
- Levine H D "Cardiac Complications of Tsutsugamushi Fever (Scrub Typhus). An Investigation of Their Persistence. *War Med* 1945 VII 76
- Norvut, L. Electrocardiogram in Typhus. *Acta med Scandinav* 1947 CXXVI 565

## Virus Diseases

- Adler E and Lyon E "Herzstörungen im Zusammenhang mit infektiöser Hepatitis". *Cardiologia* 1946-47 XI 111
- Cannell D E "Myocardial Degenerations in Yellow Fever". *Am J Path* 1978 IV 431
- Dehn H Feil H and Rinderknecht R E. Electrocardiographic Changes in Cases of Infectious Hepatitis. *Am Heart J* 1946 XXXI 183
- Dolgopol V B and Cragan M D. Myocardial Changes in Poliomyelitis. *Arch Path* 1948 XLVI 202
- Evans W F, and Graybiel A. Electrocardiographic Evidence of Cardiac Complications in Infectious Mononucleosis. *Am J M Sc* 1946 CCXI 220
- Felknor G E and Pullen R L. Mumps Myocarditis. *Am Heart J* 1946 XXXI 238
- Finland M Parker F Jr Barnes M W and Jolliffe L S. Acute Myocarditis in Influenza A Infections. Two Cases of Nonbacterial Myocarditis with Isolation of Virus from the Lungs. *Am J M Sc* 1945 CCIX 455
- Geffert W I et al "The Heart in Acute Anterior Poliomyelitis". *Am Heart J* 1947 XXXIII 228
- Gregg N M. Congenital Cataract Following German Measles in the Mother. *Tr Ophth Soc Australia* 1941 III 35
- Ludden T E and Edwards J E. Carditis in Poliomyelitis. An Anatomic Investigation of 35 Cases and Review of the Literature. *Proc Staff Meet Mayo Clin* 1948 XXIII 379 and *Am J Path* 1949 XXV 357
- Rosenberg D H. Acute Myocarditis in Mumps. *Arch Int Med* 1945 LXXVI 257
- Saphir O. Virus Myocarditis. *Mod Concepts Cardiovas Dis* 1949 XVIII No 6
- Saphir O and Wile S A. Myocarditis in Poliomyelitis. *Am J M Sc* 194 CCIII 781
- Spain D M Bradess V A and Parsonnet V "Myocarditis in Poliomyelitis". *Am Heart J* 1950 XL 336
- Swan C Tostevin A L Moore B Mayo H and Barham Black G H "Congenital Defects in Infants Following Infectious Diseases During Pregnancy With Special Reference to the Relationship Between German Measles and Cataract, Deaf Mutism Heart Disease and Microcephaly and to the Period of Pregnancy in Which the Occurrence of Rubella Is Followed by Congenital Abnormalities". *M J Australia* 1943 II, 201

Swan C Tostevin A L and Black G H B "Final Observations on Congenital Defects in Infants Following Infectious Diseases During Pregnancy with Special Reference to Rubella" *M J Australia* 1946 II 889

### Malaria

Merkel W C "Plasmodium Falciparum Malaria Coronary and Myocardial Lesions Observed at Autopsy in Two Cases of Acute Fulminating P Falciparum Infection" *Arch Path* 1946 XLI 290

Rojas R A and Deza D "Cardiac Changes in Malarial Patients" *Am Heart J* 1947 XXXIII 702

Sprague H H "The Effects of Malaria on the Heart" *Am Heart J* 1946 XXI 46

### Infestations

Arrillaga F C de Soldati L and Gandulla L "Sobre cuatro casos de miocarditis chagastica cronica" *Rev argent de cardiol* 1950 XVII 29

Baker R D and Brian E W "Blastomycosis of the Heart Report of Two Cases." *Am J Path* 1937 XIII 139

Beecher C H and Amidon E L "Electrocardiographic Findings in 44 Cases of Trichinosis" *Am Heart J* 1938 XVI 219

Carter M G and Korones S B "Amebic Pericarditis Review of the Literature and Report of a Case" *New England J Med* 1950 CCXLII 390

Chagas C and Villela E "Forma cardiaca da Trypanosomiasis Americana" *Memorias do Instituto Oswaldo Cruz* 1922 XIV No 1 Reprinted by Manguinhos Rio de Janeiro 1922

Cornell A and Shookhoff H B "Actinomycosis of Heart Simulating Rheumatic Fever Report of 3 Cases of Cardiac Actinomycosis with Review of Literature" *Arch Int Med* 1944 LXXIV 11

Cruz O and Chagas C "First description of American trypanosomiasis in Brazil 1909 (see Foreign Letters) *JAMA* 1943 CXXI 65)

Cuenca H "La miocarditis bilharziana" *Rev Cubana d Cardiologia* 1938 I 25

d'Abreu A L "Removal of a Hydatid Cyst from Wall of Left Ventricle" *Thorax* 1940 V 362

Decourt L V et al "Chronic Heart Involvement in Chagas Disease" *Am Heart J* 1947 XXVIII 697

Dobrotin A N "Drei Fälle des Echinokokkus des Herzens" *Arch Arch f path Anat* 1906 CCLXI 575

Gilmore H R Jr et al "Sarcosporidiosis with Parasites Found in Heart Case" *Am J Trop Med* 1942 XXII 121

Kyle L H McKay D G and Sparling H J "Strongyloidiasis" *Ann Int Med* 1948 XXIX 1014

Letulle M and Hufnagel M "L'Actinomycose du coeur" *Bull d l'Acad d med d Paris* 1919 LXXXII 170

MacNeal W J Blevins A and Duryee A W "Clinical Arrest of Endocardial Actinomycosis After Forty four Million Units of Penicillin" *Am Heart J* 1946 XXVI 663

Reingold I M "Myocardial Lesions in Disseminated Coccidioidomycosis" *Am J Clin Path* 1940 XV 1044

Rio Leon R "Contribucion al estudio de las manifestaciones cardiovasculares de la anquilostomiasis" *Rev Cubana d Cardiologia* 1943 IV 25

Spink W W "Cardiovascular Complications of Trichinosis" *Arch Int Med* 1915 LVI 238

Zoeckler S J "Cardiac Actinomycosis A Case Report and Survey of the Literature" *Circulation* 1951 III 854

---

## CHAPTER 18

---

### THE HEART IN THYROID DISEASE AND IN DISEASES OF OTHER GLANDS OF INTERNAL SECRETION

---

Although this chapter requires less revision since the last edition than most of the rest of the book it is like several other chapters decreasing in importance and quite likely can be eliminated altogether eventually or at least demoted to a small section in the chapter on miscellaneous etiologic relationships. This is of course due to the constantly earlier recognition and more adequate treatment of endocrine diseases before the heart and blood vessels are importantly affected.

Endocrinopathy has very little serious effect on the heart. Even that disorder which has much more influence than any other, namely thyrotoxicosis, now accounts for but a small fraction of 1 per cent of cases of heart disease in any enlightened community. However, there are many interesting and important cardiovascular and circulatory relationships and effects of the endocrine hormones, normally and abnormally. For example, the glands of internal secretion, especially the adrenal, the posterior pituitary, and the thyroid, have an important influence on the distribution of water throughout the body, partly by a direct effect on the kidney and cell permeability in general, and partly by an effect on electrolytes and metabolism of carbohydrates, protein, and fat. The adrenal and possibly the posterior pituitary play an important role in the renal control of sodium and upon its internal distribution. Transfers of sodium and potassium across cell membranes are influenced by the hormones. And now the hormones are being studied as to their striking influence on the course of certain diseases such as rheumatoid arthritis and rheumatic fever. A great deal of study remains to be done on these relationships, but they are opening up an important field which may, as a matter of fact, result eventually in a considerable revision of a book such as this. Further discussions of hormonal influences will be found elsewhere in the book, for example, later in the present chapter in the discussion of adrenal diseases and in the chapters on rheumatic fever and congestive failure.

## DISEASES OF THE THYROID GLAND

Diseases of the thyroid gland which materially affect the heart are only that which produces an excessive or toxic secretion (exophthalmic goiter or Graves disease) resulting in thyrotoxicosis, and that which is attended by a markedly decreased secretion (myxedema and cretinism)

Simple enlargement of the thyroid gland (colloid or simple or endemic goiter) causes no trouble with the heart or circulation unless the gland becomes so large that pressure on veins and arteries results in embarrassment to the entrance of blood into and its exit from the heart or compression of trachea and bronchi interferes with respiration (Rose 1878 Kocher 1902) Adenomatous goiter (struma nodosa) is much more likely to cause these disturbances than is simple colloid goiter In some parts of the world for example in the north central ( middle west ) and northwestern regions of the United States bordering on the Great Lakes and westward to the Pacific Ocean and in Switzerland colloid or simple goiter with its occasional slight secondary circulatory embarrassment is common in other parts of the world for example in New England and in other lands bordering the sea where iodine is plentiful such goiter is rare

Excessive secretion is not produced by a colloid goiter but if later in life the simple colloid goiter becomes adenomatous thyrotoxicosis may be superimposed

## THE HEART IN THYROTOXICOSIS

Thyrotoxicosis also called hyperthyroidism may result from general hyperplasia or from adenomatous goiter The term thyrotoxicosis will be used throughout the book in the place of hyperthyroidism since it indicates a toxic degree of hyperthyroidism and includes abnormal thyroid secretion if such exists as well as excessive secretion

Persistent overactivity of the thyroid gland commonly gives rise to an important but preventable type of heart trouble which has become familiarly known as the thyroid heart but which might better be called the thyrotoxic heart or the heart in thyrotoxicosis For the most part the heart as well as the circulation in general in thyrotoxicosis is simply physiologically over active pathologic changes that is real heart disease in thyrotoxicosis is relatively rare The true thyrocardiac may be said to be the individual who as a result of thyrotoxicosis has atrial fibrillation and eventually if not properly treated cardiac enlargement and congestive heart failure as a rule the evolution of a thyrocardiac is in just that order

Frequency Thyrotoxic heart disease varies in frequency both absolutely and relatively in different parts of the world not only according to the frequency of thyrotoxicosis in such parts but also according to the rapidity of diagnosis and proper treatment of the thyrotoxicosis In New England 20 to 25 years ago thyrotoxicosis was found to be a causative factor in 3 per cent of

2314 cases of organic heart disease (White and Jones 1928) in Virginia it was reported in 3½ per cent of 300 cardiac patients (Wood Jones and Kambrough 1926) while in Oregon it was found in 11 per cent of 1344 cardiac cases (Coffen 1929) in Oregon there is much more endemic (colloid) goiter than in New England and Virginia out of all proportion to the amount of thyrotoxicosis that is the endemic goiter is relatively much more frequent than the thyrotoxicosis. That thyrotoxic heart disease is preventable and is already decreasing in communities where early diagnosis and adequate treatment of the thyrotoxicosis itself are carried out is indicated by the fact that among the first 2500 patients whom I examined in consulting practice from 1920 to 1927 because of cardiac symptoms or signs there were 24 cases of heart disease due to thyrotoxicosis while among the next 2500 patients seen from 1927 to 1933 there were only 10 such cases in the third lot of 2500 private patients seen from 1933 to 1940 there were 4 cases and in the fourth such series examined from 1940 to 1946 there were but 3 thyrotoxicosis not responsible for heart disease was occasionally found throughout the entire period.

**Etiology Cause** The fundamental cause of this type of heart disease is an abnormal activity of the thyroid gland with excessive (or disturbed) secretion. The mechanism by which thyrotoxicosis produces heart disease is probably dependent on three factors which may be summarized briefly as follows. First the increased general body metabolism which results from abnormal thyroid activity increases the demand on the heart and circulation. It has been estimated that the blood flow at rest is at least 50 per cent above the normal in a case of thyrotoxicosis of average intensity and that with exercise this disproportion is still greater. The increased blood flow is due not only to the increased pulse rate but also to an increase of volume output per beat from the heart although this increase of volume output per beat is less than in a normal heart responding to exercise with the same degree of tachycardia as that found in thyrotoxicosis. The systolic blood pressure is somewhat elevated and the diastolic pressure often lowered so that the pulse pressure is frequently much increased. This constantly increased blood flow is maintained by a constant overactivity of the circulation. Such persistent overactivity tends to increase somewhat the size of the heart both in muscle (thus producing a simple work hypertrophy) and in capacity (dilatation) but cardiac enlargement is very inconstant and not the rule in the majority of cases. Eventually in some very severe prolonged cases and in those complicated by valvular heart disease hypertension or coronary disease the persistent overactivity can cause excessive strain arrhythmia and failure. A possible parallelism has been seen in experimental animals which show considerable cardiac enlargement after excessive exercise maintained during much of the time for weeks or months.

A second and more important consideration however is that practically all thyrotoxic heart disease starts with a persistent atrial fibrillation the tachycardia and arrhythmia of atrial fibrillation add to the strain of the thyrotoxicosis and tend after some years to produce cardiac enlargement which might

not have occurred from atrial fibrillation in the case of a normal heart to start with without thyrotoxicosis particularly if the ventricular rate were adequately controlled by digitalis (an impossibility in the presence of considerable thyrotoxicosis) A third factor that helps to explain the heart disease in thyrotoxicosis is that the heart itself is the seat of specific thyroid stimulation with local increased metabolism as in the case of other tissues in the body this increased wear and tear of the cells of the myocardium favoring in its turn enlargement and failure A fourth possible factor is that of a kind of arteriovenous shunt or aneurysm with blood rushing through the widely dilated vessels of the thyroid gland affording an appreciable extra burden for the heart and favoring enlargement as in the case of a traumatic arteriovenous aneurysm anywhere (Boas 1923)

An actual myocardial lesion consisting of degenerative changes at one time suggested as an important finding, has been in more recent years discounted and shown to be but an inconstant incidental occurrence (McEachern and Rake 1931 Weller and associates 1932)

A distinction so far as the heart is concerned between general glandular hyperplasia and the so called adenomatous goiter with hyperfunction (toxic adenomata) cannot be made as a rule the latter is found in older patients in whom other causes of heart strain (such as hypertension and coronary disease) are also more likely

The frequency of definite cardiac abnormality (not simply tachycardia and cardiac symptoms) in patients with thyrotoxicosis has been reported variously from a high estimate of enlargement of the heart in 50 to 60 per cent of fatal cases (McEachern and Rake 1931 Kepler and Barnes 1932) to a low estimate of only a few per cent in unselected groups atrial fibrillation in about 15 per cent and cardiac insufficiency in 5 to 10 per cent These abnormalities of the heart are much more common when there are complicating factors like hypertension

**Age** The age at which thyrotoxicosis is found varies widely, from 3 years up to 76 but the commonest age of onset is from 20 to 40 years In a series of 500 cases of thyrotoxicosis analyzed by Means and Richardson (1929) the age incidence of onset by decades was as follows first decade 3 cases second 60 third 165 fourth 147 fifth 93 sixth 29 and seventh 3 The average age was 37 years in another series of 500 cases of thyrotoxicosis (Hurxthal 1928) The age incidence of thyrotoxic heart symptoms parallels this more or less closely in a series of 68 cases 56 per cent were between 30 and 50 years old (White and Jones 1928) In a series of 108 cases of thyrotoxicosis with atrial fibrillation the average age was 51.5 years (Barker Bohning and Wilson 1932) these represent the more advanced cases on the way to serious thyrotoxic heart disease

**Sex** In thyrotoxicosis itself the female sex predominates over the male the ratio is about 5 to 1 In Means and Richardson's series (1929) of 500 cases of thyrotoxicosis there were 417 females and 83 males But the males are more severely affected and so show a relatively higher percentage of cardiac

involvement (by about 2 to 1) in a series of 34 cases of my own of thyrotoxic heart disease there were 24 women and 10 men

*Other etiologic factors* Race has little to do with thyrotoxic heart disease but in days gone by social and economic status did play a role in that inadequate financial resources did at times prevent early diagnosis and surgical correction of the thyrotoxicosis and so favored the establishment of heart disease. In thyrotoxicosis itself heredity plays a part how important we do not know

In the incidence of simple nontoxic goiter and perhaps secondarily in that of toxic goiter there is a role played by geographic factors involving iodine content of foods and water. Heart trouble due to thyrotoxicosis is more common in regions where there is much simple goiter but this is not due to the goiter itself. The change of the simple goiter later in life to adenomata which can become toxic may account for this finding

Finally the education and intelligence of both the lay and medical population determine the rapidity with which the thyrotoxicosis is detected and corrected—a factor of very great importance in the prevention of heart disease

*Pathology* There are no constant cardiovascular lesions in thyrotoxicosis. Enlargement of the heart with hypertrophy of the fibers is present in many cases especially in those with long-established atrial fibrillation but it is sometimes difficult to exclude the factors of hypertensive and coronary heart disease in these cases. In a few cases necrosis of the myocardium has been found but this finding has not been confirmed as a thyroid effect. The heart weight is generally somewhat increased to 400 or 500 gm in serious cases the average weight of the hearts of 13 fatal cases was 438 gm the two heaviest hearts weighing 530 gm each (Barker Bohning and Wilson 1932). With the onset of failure dilatation of the cavities and atrioventricular valve rings occurs but endocarditis and pericarditis are not found as a primary result of thyroid toxicity

*Symptoms* There are no characteristic symptoms of thyrotoxic heart disease. The early cardiovascular symptoms of thyrotoxicosis itself are due to the tachycardia and effort syndrome they are chiefly palpitation and dyspnea and uncommonly heartache. If atrial fibrillation or failure supervenes these symptoms increase. Palpitation is of two types (1) the forceful beating with normal heart rhythm which may be extremely unpleasant and (2) that due to paroxysmal changes in rhythm. Periods of rapid palpitation are common in thyrotoxicosis whether or not the heart is diseased they last a few minutes to a few hours and are due to paroxysms of sinoatrial or ectopic atrial tachycardia or of atrial fibrillation or flutter. Angina pectoris rarely accompanies thyrotoxicosis and then only in older persons in whom the stage is already set by the presence of coronary disease which is not sufficient in itself to give rise to the paroxysmal pain. The angina pectoris like the arrhythmia and congestive failure may be relieved by thyroidectomy when the metabolic rate is reduced thereby

*Signs* Increased heart action both in rate and force is the most common



cardiovascular sign in thyrotoxicosis and this activity is manifest on inspection palpation and auscultation over the precordium on inspection and palpation of the arterial pulse in neck and arms and on fluoroscopic examination. Enlargement of the heart congestive failure and arrhythmia when they occur show themselves in the usual way. In the early stage of the disease the heart may at first appear to be enlarged on hasty inspection and palpation because of the forceful beating against the chest wall when really it is of normal size. Cardiac hypertrophy has however been found at autopsy in the majority of fatal cases (Friedberg and Sohval 1937). A harsh unusually superficial systolic murmur is sometimes heard in thyrotoxicosis in the second and third intercostal spaces just to the left of the sternum its origin is not clear but it is probably a physiologic pulmonary murmur dependent on the increased pulmonary circulation with dilatation of the pulmonary artery reinforced by the forceful heart action and thin chest wall. This pulmonary systolic murmur has in rare cases been attended by a slight thrill. Also at times a to and fro friction rub has been noted in the region of the pulmonary conus (Goodall 1920 Lerman and Means 1932) and in very rare cases a functional aortic regurgitant murmur has also been described (Parade 1935).

Exophthalmos and thyroid gland enlargement the most common signs of thyrotoxicosis may be but little evident in some cases and the heart action may first suggest the correct diagnosis. A staring or worried look is sometimes present in the absence of frank exophthalmos. Lid lag may be present also with little exophthalmos. Bulging of the eyes unilateral or bilateral may actually be precipitated or aggravated by thyroidectomy.

In almost 80 per cent of cases of thyrotoxicosis the heart rhythm is normal and the pulse rate is fast averaging 100 to 120 per minute at rest. Rare cases have a normal or only slightly elevated pulse rate. In the remaining 20 per cent the heart rhythm is disturbed the disturbance consisting almost invariably of atrial fibrillation (noted in 207 of Ernsten's 1 000 cases 1938) of permanent nature in two thirds of the cases and of paroxysmal type in one third. In addition there are relatively infrequent cases with atrial flutter and atrial paroxysmal tachycardia.

Atrial fibrillation is commonest in the cases with congestive failure occurring in the majority of these. In one series of 111 cases of thyrotoxicosis with congestive heart failure atrial fibrillation was present in 83 per cent (Hurxthal personal communication 1930). Of 232 cases of atrial fibrillation due to thyrotoxicosis Hurxthal found that 38 per cent had also congestive failure. Thus atrial fibrillation may be considered to be but a stepping stone to congestive failure an argument against such an actual entity as thyroid myocardial disease since atrial fibrillation often occurs without evidence of disease in the heart muscle. In Ernsten's series of 1 000 cases of hyperthyroidism 44 (4.4 per cent) had congestive heart failure the two most important factors responsible for this complication were organic heart disease and uncontrolled atrial fibrillation.

The systolic blood pressure is usually somewhat elevated in thyrotoxicosis.

averaging 140 to 150 mm mercury in one quarter to one third of the cases it exceeds 150. The diastolic pressure is usually at a slightly decreased level averaging 60 to 70 mm. Thus the pulse pressure is generally increased and the arterial pulse is full.

The roentgen ray study of the heart in thyrotoxicosis shows often considerable prominence of the pulmonary artery (probably secondary to the marked increase in the pulmonary circulation) and unusually energetic rapid heart action. These two signs are together very suggestive and almost pathognomonic of thyrotoxicosis especially with the subject in the resting state. In spite of overactivity however the heart sometimes appears to be lacking in tone in the presence of thyrotoxicosis. Aortic regurgitation also gives markedly increased cardiac action in a young person especially but the considerable cardiac enlargement and the aortic diastolic murmur make the differentiation easy. The water hammer pulse is not so good a differentiating sign for in occasional cases of thyrotoxicosis with much peripheral vasodilatation there is a well marked Corrigan pulse. If cardiac enlargement is present it is best made out by roentgenologic study. Arrhythmias may be seen fluoroscopically but are not so well distinguished as by electrocardiography. Unusual clearness of the lung fields has been noted as occurring in thyrotoxicosis probably largely because of the thin chest walls of most of the patients.

The electrocardiogram shows no specific effect of thyrotoxicosis. The tachycardia and arrhythmia that may be present are readily seen but the individual complexes are otherwise normal. It was thought years ago that the *T* wave might be found unusually high because in hypothyroidism the *T* wave is always low but this has proved not to be the case. In fact in many cases the *T* waves are low and in rare cases may actually be inverted in Lead 2 (Graybiel and White 1935). Doubtless a sympathetic nervous effect. It has been shown that sympathetic stimulation contrary to early ideas lowers or inverts the *T* waves while vagus stimulation raises them (Hartwell Burrett Graybiel and White 1942).

The basal metabolic rate during the active stage of thyrotoxicosis is always high though it varies considerably with the individual case being studied. A rate of 50 to 75 per cent above normal is not infrequent. 25 to 30 per cent above normal is considered to be on the borderline and demands close scrutiny for signs of thyrotoxicosis. It must be remembered that careful technique and avoidance of excitement are essential before judgment can be passed confidently on a borderline case or even on one that shows a distinctly high rate. Also it is important that repeated basal metabolic rate determinations should all show high readings in confirmation of the diagnosis of thyrotoxicosis. One or two readings in doubtful cases are inadequate. Congestive heart failure alone may definitely raise the basal metabolic rate to about +30 per cent apparently as the result of increased work occasioned by the labored breathing. It has been reported as high as 40 to 50 per cent above normal though such increase is unusual. The pulse rate, pulse pressure and blood flow are all usually increased proportionally to the rise of the basal metabolic rate. All

though operative relief or spontaneous remission of active thyrotoxicosis may occasionally leave behind some cardiac involvement especially atrial fibrillation symptoms and signs usually subside along with the metabolic rate. It should be added that very rare cases of thyrotoxicosis may have basal metabolic rates within the normal range (0 to +10 per cent for example) such patients probably represent the small group of individuals who normally show low rates (-20 to -30 per cent) without myxedema. Thus all evidence is necessary besides the basal metabolic rate in difficult diagnostic cases.

Two more specific tests for thyrotoxicosis than the basal metabolic rate have been introduced in the past few years they consist of (1) the measurement of the protein bound iodine in the blood which should normally not exceed 7.5 to 8.0 gamma per cent and (2) the calculation of radioactive iodine ( $I^{131}$ ) uptake by the thyroid gland which should normally not exceed 50 per cent but which in thyrotoxicosis is much increased. This latter test is much more accurate than either the former or the basal metabolic rate determination.

One of the most important of all diagnostic clues is the rapid and favorable response of true thyrotoxicosis to iodine therapy.

**Course and prognosis** The course and prognosis of thyrotoxic heart disease are extremely variable and depend on the severity and duration of the thyrotoxicosis. The abnormal condition of the heart may be scarcely noticeable and with the clearing up of the cause of trouble occasion no further symptoms and few or no signs. With very severe thyrotoxicosis that has lasted for a long time heart disease may be evident by the presence of enlargement, atrial fibrillation and congestive failure but there are infrequent exceptions when the heart may appear to be perfectly normal even after a good many years. The usual case of average toxicity shows in the course of years heart changes that are more than functional if there is no operative relief or spontaneous remission death from heart failure may ensue in such cases after a few more years. Of a series of 178 fatal cases of thyrotoxicosis 27 showed severe congestive failure in 9 of which no other factor could be found than the thyrotoxicosis alone (Kepler and Barnes 1932). Other complications such as pneumonia may intervene to end the story. Now and again in wasted and pigmented aged individuals chronic heart disease can be traced back to a former thyrotoxic state but is very likely to be wrongly interpreted as "arteriosclerotic" if the thyrotoxicosis is still active in these cases operation or other specific therapy should be carried out and may be expected to afford considerable relief.

It is to be noted that thyrotoxicosis tends to recur after subtotal thyroidectomy in about 10 per cent of the cases (Greene and Hurxthal 1941) hence the return of atrial fibrillation or other signs or symptoms during the years following operation should make one think of this possibility.

**Complications** The commonest cardiac complication of thyrotoxicosis is atrial fibrillation which may occur at first as a functional disturbance alone.

with little or no actual heart disease. In the late stages of thyrotoxic heart disease congestive failure may supervene. It is of much interest that in thyrotoxicosis as in beriberi the cardiac output may continue to be increased well above the normal despite the presence of considerable congestive heart failure with elevated systemic venous pressure.

Chronic rheumatic valvular disease is an occasional complication of thyrotoxicosis and atrial fibrillation may lead to a diagnosis of one or the other condition when both are present. Coronary heart disease may be another complication in the older cases and the combination may produce angina pectoris. Hypertension of high grade may also occur (in about 10 per cent of the cases) the systolic blood pressure in thyrotoxicosis itself rarely exceeds 160 mm mercury.

**Treatment** The treatment of the heart condition resulting from thyrotoxicosis is fourfold: (1) therapy of the thyrotoxicosis, (2) therapy of heart failure, (3) therapy of atrial fibrillation and (4) observation for recurrence of abnormal thyroid activity.

The first of these therapeutic procedures, namely the treatment of the thyrotoxicosis, comes foremost in the consideration of almost every case because not only does this therapy control the cause of trouble but it actually may relieve without further therapy either or both of the serious complications, congestive failure and absolute arrhythmia.

After careful trial of other methods of treatment of active thyrotoxicosis (either ordinary exophthalmic goiter or adenomatous goiter) ■ good many authorities (e.g. Means et al. personal communication 1951) still believe that the best therapy in the present state of our knowledge is subtotal thyroidectomy. Rest in bed and roentgen irradiation, though they have been apparently effective in some mild cases, are far less dependable in the long run and any delay of proper treatment may do harm.

A useful measure in the preparation of patients for operation has been the administration of iodine for one to two weeks, for example potassium iodide 5 gr (0.3 gm) once daily in saturated solution, the 5 minims or grains containing  $330 \pm$  mg of iodine, or Lugol's solution 10 minims (0.60 cc) containing 60 mg of iodine three times ■ day for ten days. Iodine promotes the storage of thyroglobulin in the follicles and places a barrier in the way of escape of hormone from the gland (Lerman and Salter 1936) hence the high basal metabolic rate, the fast pulse rate and all the symptoms of thyrotoxicosis are much abated and the patient is a better risk for operation. Iodine therapy alone is not sufficient to control the thyrotoxicosis constantly except in a few mild cases. It has also been shown that thiouracil will control the basal metabolic rate prior to operation in the dosage of 300 mg of propyl thiouracil daily and divided into three doses given eight hours apart. This is continued until there has been much improvement in the patient's condition at which time ■ is wise to give 5 to 10 drops of saturated solution of potassium iodide daily for ten days along with the thiouracil ending with the surgical operation. Thi-

ouracil and related preparations have in some cases been used successfully in controlling thyrotoxicosis without operation, however toxic effects especially on the blood limit its use

Shortly after operation when the occasional stormy reaction has subsided it is usually discovered that the heart condition is much improved if not and the thyrotoxicosis continues further treatment may be necessary With careful preparation and the expert anesthesia and surgery that are essential for the best results remarkable benefits have been frequently secured even in cases which were apparently hopeless because of heart failure and which have been considered generally as poor operative risks The relief of the thyrotoxicosis in such cases has proved far more important in the relief of the heart trouble than have remedies like digitalis and rest in bed directed to aid the heart condition alone It is to be noted further that iodine has far more effect than digitalis in reducing the pulse rate in the tachycardia of thyrotoxicosis per se in fact digitalis is almost invariably ineffective in this respect while iodine is nearly always at first effective

An ingenious therapeutic technic recently introduced for thyrotoxicosis consists of the use of irradiated iodine (I-131) orally adequate control of the disease has been effected without surgery a desirable achievement in cases where the cardiac status is precarious Incidentally as will be noted in the chapters on Coronary Heart Disease (Chapter 21) and on Congestive Heart Failure (Chapter 30) irradiated iodine (I 131) has been used effectively by Blumgart et al (1948) to control both coronary and myocardial insufficiency through the production of a medical thyroidectomy

The therapy of the heart failure due to thyrotoxicosis consists primarily as noted above in the control of the thyrotoxicosis itself by the administration of iodine and operation rest digitalis and diuretics are additional therapeutic measures not very effective however, until the high metabolic rate has been reduced The tolerance of thyrotoxic patients for digitalis is usually quite marked and the therapeutic dose of this drug must be proportionately increased sometimes as much as 50 to 100 per cent above the ordinary dosage in order to obtain any appreciable effect whether beneficial or toxic but only under careful observation

The third therapeutic measure consists of treatment of the atrial fibrillation that may complicate thyrotoxicosis There is little likelihood of control of this arrhythmia while thyrotoxicosis persists but there is a fair chance almost an even chance that relief of the thyrotoxicosis alone will relieve also the atrial fibrillation If it does not do so quinidine will restore normal rhythm in about half of the remaining postoperative cases in whom this arrhythmia persists, while digitalis can be used permanently to control the ventricular rate in the rest of the cases with persistent atrial fibrillation The method of administering digitalis and quinidine will be discussed in Chapters 30 and 33 of this book For paroxysms of atrial fibrillation either before or after thyroidectomy rations of quinidine sulfate (3 to 6 gr 0.18 to 0.36 gm three or four times daily) may be tried they are more likely to be successful after operation

**Differential diagnosis** Thyrotoxicosis as a cause of cardiac enlargement failure and atrial fibrillation must be differentiated particularly from rheumatic heart disease and essential hypertension. Moreover when patients presenting obvious signs of rheumatic or hypertensive heart disease with congestive failure do not obtain relief from the usual therapeutic methods thyrotoxicosis should be suspected as a possible complication.

The early stage of thyrotoxicosis before definite cardiac signs have developed is especially to be distinguished from neurocirculatory asthenia. Its differentiation is not always a simple matter; it is sometimes impossible when the basal metabolic rate is at the normal borderline and there is no definite exophthalmos or thyroid gland enlargement—most of such cases prove later not to have any definite thyrotoxicosis. The differential diagnosis requires especial care if one has to deal with a patient who has both neurocirculatory asthenia and a colloid goiter.

Rare atypical cases with overactive thyroid glands are found without exophthalmos or goiter; a slight staring anxious expression, unexplained loss of weight, diarrhea, pigmentation of the skin and tachycardia may afford clues. When in doubt the basal metabolic rate should always be determined and repeated as often as necessary, and especially the protein bound iodine in the blood should be determined (normal = 4.0 to 8.0 gamma per cent) or the radioactive iodine uptake (normal = 20 to 50 per cent at the end of 48 hours). Finally a therapeutic test with iodine may be carried out (Means 1937).

### HYPOTHYROIDISM MYXEDEMA HEART

The state of underactivity of the thyroid gland consisting typically of myxedema in adults and of cretinism in children is an infrequent condition itself and a still rarer cause of appreciable heart disease. However in almost every case some abnormality of cardiac function is evident in the sluggish heart action and especially in the uniform flattening or inversion of all the T waves of the electrocardiogram (Figure 92A, page 454); these abnormalities are corrected by thyroid therapy (Figure 92B). Enlargement of the x-ray heart shadow, sometimes at least due to pericardial effusion, is also a usual finding in severe myxedema; in some cases it is very striking while in others due to the wide range of the normal heart size it may become evident only in the process of taking serial roentgenograms. It generally subsides under thyroid treatment with astonishing speed and degree (Figure 93, page 455). Arteriosclerosis likewise is frequent in myxedema.

The term myxedema heart has been applied to a condition found in about three quarters of the cases of myxedema (Zondek 1918, 1919, Fahr 1925, 1927, 1932, Fournier 1942) and this will be described below. In many cases of myxedema, however, especially the milder ones, it is difficult or impossible to make out any important abnormality of the heart caused directly by this glandular deficiency. The cretin too has no very definite heart disease but

shows as in myxedema, abnormal electrocardiographic *T* waves and sluggish cardiac action

**Etiology Cause** It is evidently the lack of sufficient thyroid secretion in myxedema which occasionally causes definite heart trouble in the form of enlargement or weakness or pericardial effusion for the administration of rations of thyroid gland corrects this trouble. In what way the hypothyroidism causes this cardiac abnormality, and what other factors may favor this effect we do not know.

Myxedema itself is usually of unknown origin but infrequently it follows thyroidectomy which is carried out to cure thyrotoxicosis. Myxedema was intentionally produced about 18 years ago in a new treatment of intractable angina pectoris and myocardial insufficiency by the surgical operation of total thyroidectomy (see Chapters 21 and 30) but this form of treatment was

Lead

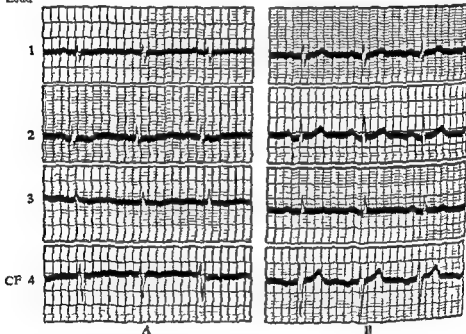


FIG 92 Electrocardiograms (four leads) in hypothyroidism (myxedema) male age 59 (A) before and (B) after thyroid therapy. Basal metabolic rate at time of (A) = -46 per cent and at time of (B) = -17 per cent

found impracticable and given up. However there has been recently a revival of the principle of therapy involved in the form of a medical thyroidectomy via irradiated iodine with prevention of any high degree of hypothyroidism by the administration of small doses of thyroid.

**Age** The myxedema heart like myxedema itself has been found usually in middle age or later but it may occur in youth. It is likely that a complication such as coronary heart disease coming independently or favored by the myxedema may help to account for the greater frequency of cardiac dilatation and weakness among the older victims of myxedema.

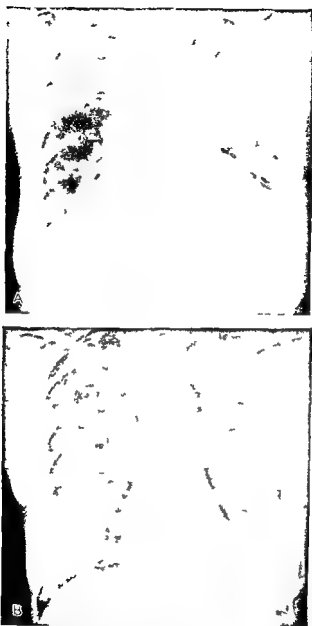


FIG 93 Roentgenograms showing great change in cardiac area (6 cm in the transverse diameter of the heart shadow) as the result of the successful treatment of myxedema by thyroid administration Woman 66 years old

(A) Dec 5 1934 basal metabolic rate =  $-46$  per cent

Cardiothoracic ratio in roentgenogram =  $\frac{18.2}{24.0}$

(B) May 21 1935 basal metabolic rate =  $-13\frac{1}{2}$  per cent

In this record the diaphragm is somewhat lower than in the former which exaggerates slightly the difference in size of the heart shadow

Cardiothoracic ratio  $\frac{12.2}{23.0}$

(Kindness of Dr J C Gant Madison College Tennessee)



*Sex* Sex has no particular relationship to the myxedema heart so far as we know

*Other factors* The most important factors controlling the incidence of the myxedema heart in any community are undoubtedly first the frequency of myxedema itself in that community, and second the ability of the medical profession to recognize and properly to treat it. It undoubtedly is a preventable type of heart disease.

*Pathology* An occasional finding in myxedema is considerable globular enlargement of the x ray heart shadow giving rise to the so-called myxedema heart. The exact cause of such enlargement is not always clear and has been a subject of some controversy, probably it is the result partly of dilatation partly perhaps of the increased bulk due to the myxedematous state affecting the heart tissues and certainly sometimes to an excess of fluid in the pericardium. All three factors may play a role in increasing the area of percussion dullness or the roentgen ray heart shadow. Functional regurgitation through the atrioventricular valves may occur with the dilatation but there is no endocarditis. Pericarditis is not found despite the occasional discovery of large pericardial effusions; the heart itself may show no actual enlargement in the midst of a large pericardial effusion. Presenile arteriosclerosis especially involving the coronaries is reputed to be a general accompaniment of myxedema but convincing evidence of this is still lacking.

*Symptoms* There are few symptoms of the heart involvement in myxedema; the low level of activity in this condition probably preventing the cardiac dilatation and weakness from making themselves more evident. Dyspnea has been noted in rare cases of congestive failure in myxedema and in a few patients with myxedema angina pectoris has occurred. These symptoms occurring at the height of the endocrinopathy itself are sometimes cleared by thyroid therapy but sometimes induced or aggravated by the specific treatment which raises the metabolism and blood flow too rapidly, coronary disease or other factors preventing the heart itself from keeping pace with the demands thus newly thrown upon it.

*Signs* The only cardiovascular signs in the case of the myxedema heart are the occasional enlargement evident both on physical examination and by roentgen ray study (Figure 94) the sluggish heart action commonly observed in the same way and the constant finding of absence or inversion of the T wave in all leads of the electrocardiogram (Figure 93). This electrocardiographic sign is almost pathognomonic of myxedema and can be used along with the determination of the basal metabolic rate in following the progress of thyroid therapy. There is frequently also a decrease in amplitude (low voltage) of the other complexes of the electrocardiogram the P and QRS waves which resume along with the T waves a more normal extent of excursion on treatment.

The usual signs and symptoms of myxedema are generally obvious—slowed mental state, dryness and thickening of hair and skin, puffiness of subcutaneous tissue (myxedema) all over the body including the face, weakness and dislike of cold. The basal metabolic rate is generally reduced to 30 per cent below

the average normal or lower borderline cases with measurements of basal metabolic rate of minus 10 to minus 25 per cent are less likely to have heart trouble and usually these individuals have not true myxedema to start with

Also in myxedema a decrease has been found in the cardiac output, circulatory velocity, peripheral flow, and total volume of blood

**Course and prognosis** The finding of evidence of significant cardiac involvement in myxedema is an important sign for it means that the grade of myxedema is a serious one or that other heart trouble such as coronary or hypertensive is present. The discovery of cardiac enlargement is usually an incidental one in the course of routine examination but it should always be looked for and the cardiac response to the treatment of myxedema should be carefully followed. Sudden death with or without angina pectoris may occur a few months or years after the finding of the myxedema heart. Death postponed by careful thyroid therapy may come eventually from other complications without cardiac responsibility in fact a full length of life is possible under careful treatment. Congestive failure as a cause of death in myxedema per se is very rare. I myself have never seen a case.

**Complications** Angina pectoris due to coronary disease is the most important complication of the myxedema heart especially after treatment of the myxedema has begun. The elevation of metabolism by thyroid therapy may induce symptoms of coronary insufficiency. Acute infections like pneumonia may appear as complications with serious prognosis. General arteriosclerosis is common but not essential.

**Treatment.** Digitalis has no definite beneficial influence on the cardiac enlargement or electrocardiographic abnormalities of myxedema. Thyroid gland on the other hand has a striking effect clearing up these conditions more or less completely if given in sufficient dosage. An amazing decrease in heart or pericardial size may sometimes be effected. In four cases of Lerman, Clark and Means series (1933) for example the transverse diameter of the heart shadow by teleroentgenogram decreased in the first case from 19.3 to 12.4 cm in six months, in the second from 21.4 to 15.7 cm in six weeks, in the third from 16.5 to 11.4 cm in eight and one half months and in the fourth from 19.4 to 15.5 cm in five months.

Thyroid gland should be given very cautiously in the treatment of myxedema particularly when there is a history of angina pectoris for although marked general improvement may ensue and the heart resume practically normal size angina pectoris may be precipitated or increased by the raised level of metabolic rate and increased blood flow and sudden death may occur just when the myxedema itself is under control. It may be necessary to give doses of thyroid so small that although the basal metabolic rate is not restored completely to normal angina pectoris is kept away or under partial control. Some myxedematous signs and symptoms may remain but life is prolonged. A dose of  $\frac{1}{4}$  to 1 gr (0.015 to 0.03 gm) of thyroid (USP) daily may accomplish this instead of the usual larger doses (1 to 2 gr). Rarely the thyroid therapy banishes angina pectoris. Digitalis should be given if there are in addition to the dilatation of the heart signs and symptoms of congestive failure.

which do not yield to thyroid therapy alone but morphine is contraindicated

**Differential diagnosis** The myxedema heart must be differentiated from cardiac enlargement and weakness of other cause, from coronary heart disease and from infectious pericardial effusion. This is usually readily done by the absence of cardiac symptoms of chronic valvular disease, and of hypertension by the typical electrocardiographic findings by the general signs of myxedema and by the response to thyroid therapy

### DISEASES OF OTHER GLANDS

**Parathyroid disease** Little is to be said of the effect of parathyroid disease on the heart. The decreased calcium content of the blood in tetany is associated with increase of the duration of cardiac systole, hyperparathyroidism and the administration of excessive amounts of parathormone cause by the increase of calcium content of blood an increase of calcium in the tissues likewise including the heart muscle. We have no proof that these results are of any clinical significance.

**Pituitary disease** The only association of abnormality of the heart with pituitary disease is the finding of cardiac enlargement (hypertrophy) especially of the left ventricle in acromegaly such enlargement may be great and out of proportion to the general splanchnomegaly found in this condition. Whether it is the result of the somewhat increased basal metabolic rate in this disease or due to other factors is not known. In one series of 24 patients marked heart failure was noted in 18 (75 per cent) six of this group died from that cause (Mason, 1936-1938). In gigantism the heart is not affected but bears a normal relationship to body size (Zondek, 1920).

Basophilia of the posterior lobe of the pituitary gland has been noted in certain cases of pituitary adenoma with hypertension and in some patients with hyperpiesia and eclampsia (Cushing, 1934) this finding has not been confirmed however as a characteristic occurrence in essential hypertension.

**Adrenal disease** Adrenal disease has a direct effect on the heart as well as on the circulation. Destruction of adrenal tissue (cortex) as in Addison's disease causes collapse marked hypotension and general muscular weakness including myocardial weakness but not structural heart disease. The heart is smaller than normal both in volume and weight in part the result of the decreased amount of circulating blood and in part due to myocardial atrophy and the T waves of the electrocardiogram are depressed.

Relief of the symptoms and signs of Addison's disease has been effected by adrenal plus sodium chloride therapy but the new specific therapy of adrenal insufficiency (Addison's disease) with desoxycorticosterone and cortisone must be followed with great care since serious cardiac enlargement and weakness may appear with toxic doses. In fact measurement of heart size has been suggested as an objective check on large dosage of the hormone (McGavack, 1942) it has been found that the dose of desoxycorticosterone acetate necessary to produce a given degree of cardiac enlargement varies inversely as the amount of sodium available in the tissues.

Not only may dilatation of the heart result from excessive desoxycorticosterone therapy of Addison's disease but even high degrees of congestive failure along with changes in the electrocardiogram which recede or disappear when the drug is omitted. The tendency to low voltage of the QRS and T waves found with Addison's disease is much exaggerated by excess of desoxycorticosterone (Currens and White 1944). These changes in the heart are probably due to or at least associated with a loss of body potassium. Illustrations of the changes in the electrocardiogram and roentgen picture of the heart due to excessive desoxycorticosterone therapy are shown in Figure 94 on page 460.

The stimulation that results from an adrenal medullary tumor (*pheochromocytoma*) can cause hypertension of paroxysmal nature which may be cured by removal of the tumor. If the hypertension is sustained however removal of the tumor may have no effect on it, splanchnic resection then being required. The tumor may be located in tissue outside the adrenal glands themselves and then may be found with difficulty.

Cortical adenomas of the adrenal may also play a role in hypertension; they are more numerous than pheochromocytomas but their removal may not have any important effect on the hypertension present in such a case (Smithwick personal communication 1942).

**Pancreatic disease.** *Diabetes mellitus* does not cause heart disease directly but it does favor arteriosclerosis and coronary artery disease (Root, Bland, Gordon and White 1939). At least 50 per cent of all diabetics die as a result of cardiovascular complications and the relative incidence of this cause of death is steadily increasing as other fatal complications are eliminated. Marked atherosclerosis of the aorta with considerable dilatation is common. Hypertension plays an important role in this group and frequently precedes the onset of the diabetes, sometimes by several years. Congestive failure due to hypertension or to coronary disease is not unusual but death comes most frequently from coronary occlusion (West 1935).

Excess of insulin does not apparently affect the heart seriously unless there is already heart disease; the possible harmful effect from insulin shock (*hyperinsulinemia*) however makes it advisable to use insulin cautiously in the presence of acute coronary thrombosis, very severe angina pectoris and congestive failure. Arrhythmias and electrocardiographic abnormalities following the use of insulin occur.

**Thymic disease.** Hypertrophy or persistence of the thymus gland is not attended by heart disease but is accompanied by general arterial hypoplasia. The cause of the sudden death in the so-called status lymphaticus and its reputed relationship to the thymus gland are still unsolved mysteries. The enlarged gland in child or adult is to be differentiated on physical examination and by roentgen ray from abnormalities of the great vessels.

**Genital glands.** Heart disease does not result from disease of ovaries or testes but functional disorders with cardiovascular symptoms of neurocirculatory asthenic type are commonly found especially at the time of the menopause in women or following double oophorectomy. Hypertension of the essential type is also a frequent finding often but temporary at the time of

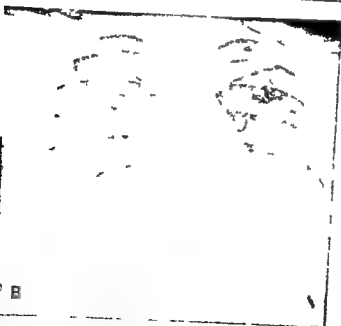
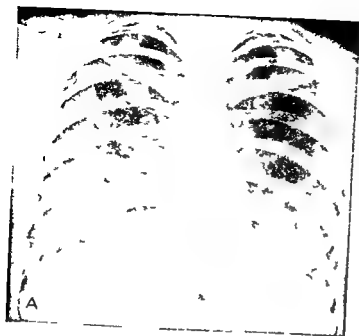


FIG 94 Roentgenograms and electrocardiograms in the case of a young woman with Addison's disease showing the toxic effect of excessive desoxycorticosterone acetate in treatment (A) Roentgenogram of the thorax Aug 13 1942 showing normal heart size and some prominence of the shadow of the pulmonary artery (B) Roentgenogram of the thorax Sept 9 1942 showing marked enlargement of the heart during the height of the effects from the desoxycorticosterone (C) Electrocardiogram more or less normal of this patient on Oct 24 1942 after the effects of the desoxycorticosterone had worn off (D) Electrocardiogram on Aug 30 1942 at the height of the toxic effect of the desoxycorticosterone

the menopause and this may affect the heart secondarily to cause hypertrophy. Hamilton (1940) has not found however that the climacteric exerts any very severe strain on the heart of women already affected by heart disease. A so-called fibroid heart has been said to result from uterine fibroid disease (fibroma) but there is no proof that such a condition exists, functional disturbances as noted above and premature beats undoubtedly accounting for this condition. There has as yet been demonstrated no real "myoma heart" (von Jaschke 1933). A change in the electrocardiogram consisting of a digitalis like depression of the ST segments and T waves, as noted by Scherf (1940) in some females with ovarian dysfunction and was cleared by estrogenic hormone therapy such changes are however rarely more than slight in degree and it is probable that some factor such as hyperventilation (see Chapter 9) secondary to the climacteric rather than the ovarian dysfunction itself is responsible.

## BIBLIOGRAPHY

## THE HEART IN THYROID DISEASE AND IN DISEASES OF OTHER GLANDS OF INTERNAL SECRETION

## Thyroid Disease Thyrotoxicosis

- Barker P S, Bohning, A. L. and Wilson F N. "Auricular Fibrillation in Graves Disease." *Am Heart J* 1932 VIII 1,1
- Blumgart H L, Freedberg A S and Bula P. "Treatment of Euthyroid Cardiac Patients by Producing Myxedema with Radioactive Iodine." *Proc Soc Exper Biol & Med* 1948 LVII 190
- Blumgart H L, Gargill S L and Gilligan, D R. "Studies on the Velocity of Blood Flow VIII The Circulatory Response to Thyrotoxicosis." *J Clin Investigation* 1930 IX, 69
- Boas E. P. "Cardiac Disorders Accompanying Exophthalmic Goiter. Some Factors in Their Pathogenesis." *JAMA* 1923 LXXX 1683
- Bortin M M and Yohalem S B. "Thyrotoxicosis Factitia Masked as Heart Disease." *Am Heart J* 1950 XXXIX 894
- Coffen, T H. "The Incidence of Heart Disease in the Pacific Northwest." *Am Heart J* 1929 V 99
- Ernstene A. C. "The Cardiovascular Complications of Hyperthyroidism." *Am J Med Sc* 1938 CXCI 248
- Freedberg, C N. and Sohval A R. "The Occurrence and the Pathogenesis of Cardiac Hypertrophy in Graves Disease." *Am Heart J* 1937 XIII 599
- Goodall J S. "The Heart in Graves Disease." *Practitioner* 1920 CX 37
- Gordon E S and Albright C C. "Treatment of Thyrotoxicosis with Radioactive Iodine." *JAMA* 1950 CXLIII 1129
- Graybiel A and White P D. "Inversion of the T Wave in Lead I or II of the Electrocardiogram in Young Individuals with Neurocirculatory Asthenia, with Thyrotoxicosis in Relation to Certain Infections and Following Paroxysmal Ventricular Tachycardia." *Am Heart J* 1935 X 345
- Greene A M and Hursthal L M. "A Postoperative Follow up Study of Four Hundred and Sixty Nine Thyrocardiac Patients." *New England J Med* 1941 CCXXV 811
- Hamilton H E. "Heart Failure of the Congestive Type Caused by Hyperthyroidism." *JAMA* 1924 LXXXIII 405
- Hartwell A S, Burrett, J B, Graybiel, A and White P D. "The Effect of Exercise and of Four Commonly Used Drugs on the Normal Human Electrocardiogram, with

- Particular Reference to T Wave Changes *J Clin Investigation* 1942 XXI 409
- Hurxthal L M "Heart Failure and Hyperthyroidism with Special Reference to Etiology" *Am Heart J* 1928 IV 103
- Jaffe H L and Ottoman H E "Evaluation of Radioiodine Test for Thyroid Function." *JAMA* 1950 CXLIII 515
- Kepler E J and Barnes A R "Congestive Heart Failure and Hypertrophy in Hyperthyroidism A Clinical and Pathological Study of 178 Fatal Cases" *Am Heart J* 1932 VIII 102
- Kocher A "Ueber Morbus Basedow" *Mitt am d Gren egeb d Med u Chir* 1907 IX 1
- Lahey F H "End Results in Thyrocardiacs" *Ann Surg* 1929 XC 750
- Lerman J and Means J H "Cardiovascular Symptomatology in Exophthalmic Goiter" *Am Heart J* 1932 VIII 55
- Lerman J and Salter W T "The Behaviour of Natural and Artificial Thyroid Protein. An Attempt at Biochemical Interpretation of the Effect of Iodine in Thyroid Disease" *Tr Am A Study of Goiter* 1936 143
- McEachern D and Rake G "Study of Morbid Anatomy of Hearts from Patients Dying with Hyperthyroidism" *Bull Johns Hopkins Hosp* 1931 XLVIII 273
- Means J H "The Thyroid and Its Diseases" J B Lippincott Co Philadelphia 2nd ed 1948 (1st ed 1937)
- Means J H and Richardson E P "The Diagnosis and Treatment of Diseases of the Thyroid" Oxford University Press New York 1929
- Parade G W "Relative Aorteninsuffizienz bei Morbus Basedow" *Deutsch med Wchnschr* 1935 LXI 1799
- Rose E "Ueber den Kropf und die Radicalcur der Kropfe" *Arch f klin Chir* 1878 XXII 1
- Stewart H J and Evans W F "The Peripheral Blood Flow in Hyperthyroidism" *Am Heart J* 1940 XX 715
- Trousseau A "Exophthalmic Goitre" Lecture 38 on *Clinical Medicine* translated from the 3rd French edition (Paris 1867) by Sir John Rose Cormack and P Victor Bazire Lindsay & Blackiston Philadelphia 1873
- Weller C V, Wanstrom R C, Gordon H and Bugher J C "Cardiac Histopathology in Thyroid Disease Preliminary Report" *Am Heart J* 1932 VIII 8
- White P D and Jones T D "Heart Disease and Disorders in New England" *Am Heart J* 1928 III 302
- Wood J E Jr, Jones T D and Kimbrough R D "The Etiology of Heart Disease Clinical Study of 623 Cases with Certain Observations on Race and Climate" *Am J M Sc* 1926 CLXXII 185

### Myxedema and Cretinism

- Blumgart H L, Gargill S L and Gilligan D R "Studies on the Velocity of Blood Flow. XIV The Circulation in Myxedema with a Comparison of the Velocity of Blood Flow in Myxedema and Thyrotoxicosis" *J Clin Investigation* 1930 IX 91
- Burgess A M "Myxedema Controlled by Thyroid Extract for 52 Years" *Ann Int Med* 1946 XXV 146
- Bustamante Marcaida R and Perez Stable Carreno E "Derrame pericardico en el corazón mixematoso" *Rev cubana de cardiol* 1949 X 205
- Fahr G "Myxedema Heart" *JAMA* 1925 LXXXIV 345 *Am Heart J* 1927 III 14 and 1937 VIII 91
- Fournier J C M "The Circulatory Apparatus in Myxedema" *Proc Staff Meet Mayo Clin* 1947 XVII 212
- Kern R A, Soloff L A, Snape W J and Bello C T "Pericardial Effusion A Constant Early and Major Factor in Myxedema Heart" *Tr A Am Physicians* 1948 LXI 158 *Am J M Sc* 1949 CCXVII 609
- Lerman J, Clark R J and Means J H "The Heart in Myxedema Electrocardiograms and Roentgen Ray Measurements Before and After Therapy" *Ann Int Med* 1933 VI 1251
- Paddock F K "Massive Ascites Due to Myxedema Report of a Case" *New England J Med* 1950 CCXLII 872

- Thacher C "The Electrocardiogram in Cretinism and in Mongolian Idiocy" *Am J Dis Child* 1934 XXVIII 25
- Thacher C and White P D "The Electrocardiogram in Myxedema" *Am J Med Sc* 1936 CLXXI 61
- Zondek H "Das Myxoderm Herz" *Munch med Wchnschr* 1918 LXV 1180 *ibid* 1919 LXVI 681

## Other Endocrine Disorders

- Courville C B and Mason V R "The Heart in Acromegaly" *Arch Int Med* 1938 LXI 704
- Currens J and White P D "Congestive Heart Failure and Electrocardiographic Abnormalities Resulting from Excessive Desoxycorticosterone Acetate Therapy in the Treatment of Addison's Disease" *Am Heart J* 1944 XXVIII 611
- Cushing H "Hyperactivation of the Neurohypophysis as the Pathological Basis of Eclampsia and Other Hypertensive States" *Am J Path* 1934 X 145
- Hamilton, B E "The Influence of the Character of the Course of Organic Heart Disease" *Proc New England Heart A* 1940-41 p 29
- Hench P S, Kendall E C, Slocumb C H and Polley H F "The Effect of a Hormone of the Adrenal Cortex (17 Hydroxy 11 Dehydrocorticosterone Compound E) and of Pituitary Adrenocorticotrophic Hormone on Rheumatoid Arthritis Preliminary Report" *Proc Staff Meet Mayo Clin* 1949 XXIV 181
- Hejlskov M R et al "Acromegaly and the Heart" *Ann Int Med* 1951 XXXIV 1445
- Holler J W "Potassium Deficiency Occurring During the Treatment of Diabetic Acidosis" *JAMA* 1946 CXXXI 1186
- Kyle L H and Knop C Q "Simulation of Cardiac Disease by Adrenocortical Failure in Infant" *New England J Med* 1950 CCXLIII 681
- Lisa, J R et al "Arteriosclerosis with Diabetes Mellitus A Study of the Pathologic Findings in 193 Diabetic and 2250 Non Diabetic Patients" *JAMA* 1944 CXX 192
- McGavack T H "The Size of the Heart as a Guide to the Treatment of Addison's Disease with Desoxycorticosterone Acetate" *Am Heart J* 1944 XXIV 99 and 1945 XXVII 331
- Martin H E and Wertman M "Electrolyte Changes and the Electrocardiogram in Diabetic Acidosis" *Am Heart J* 1947 XXIV 646
- Mason V R "The Heart in Acromegaly" *Tr 4 Am Physicians* 1936 LI 220
- Nadler C S, Bellet, S and Lanning M "Influence of the Serum Potassium and Other Electrolytes on the Electrocardiogram in Diabetic Acidosis" *Am J Med* 1949 V 838
- Neubauer R A and Frelick R W "Spontaneous Hyperkalemia as a Cause of Death in Diabetic Acidosis" *Am Heart J* 1950 XL 793
- Raab W "Cardiovascular Effects of Desoxycorticosterone Acetate in Man" *Am Heart J* 1944 XXIV 365
- Root, H F, Bland E F, Cordon W H and White P D "Coronary Arteriosclerosis in Diabetes Mellitus A Postmortem Study" *JAMA* 1939 CXIII 27
- Saks H A "Crisis in Addison's Disease Simulating Coronary Thrombosis" *Illinois M J* 1937 LXXI 475
- Scherf D "The Respiratory and the Circulatory System in Females with Ovarian Dysfunction" *Ann Int Med* 1940 XIII 1414
- Somerville W et al "Electrocardiogram in Addison's Disease" *Medicine* 1951 XXX 43
- Thorn G W, Dorrance B S and Day E "Addison's Disease Evaluation of Synthetic Desoxycorticosterone Acetate Therapy in 158 Patients" *Ann Int Med* 1944 XVI 1053
- Thorn G W, Nelson K R and Thorn B W "Study of Mechanism of Edema Associated with Menstruation" *Endocrinology* 1938 XXII 155
- von Jaschke R T "Der Zirkulationsapparat beim Myom" *Arch f Gyn* 1933 CLV 6
- West H F "Diabetes and Cardiovascular Disease" *Mod Concepts Cardiovas Dis* 1935 IV No 1
- Zondek H "Herzgefunde bei endokrinen Erkrankungen" *Deutsch med Wchnschr* 1930 XLVI 1239



## HYPERTENSIVE HEART DISEASE ESSENTIAL HYPERTENSION HYPOTENSION

### HYPERTENSIVE HEART DISEASE

**Introduction** Since the last revision of this book seven years ago there have been innumerable studies and published reports concerning hypertension and hypertensive cardiovascular disease many of them of considerable interest and value, as may be observed on perusal of the additions of references to representative publications in the Bibliography at the end of the chapter. Nevertheless the mechanism of the so-called essential type of hypertension still eludes us; another few years may very well reveal to us the answer, or the answers, since so many able workers are engaged on the problem. Meanwhile to date distinct advances in therapy, though empirical, have been scored.

The most common and important of all types of heart disease by and large the world over is that due to systemic hypertension with elevation of the diastolic blood pressure. It is often serious and frequently followed by congestive failure and death. It has been estimated that nearly 100 000 people die annually in the United States (population of about 130 000 000) as the result of heart failure due to hypertension and that 7 000 more die from other consequences of high blood pressure. In a series of 30 265 autopsies with 4 678 cardiovascular deaths (15.45 per cent) 2 597 were hypertensive cases (55.5 per cent of the cardiovascular deaths and 8.6 per cent of the total autopsies); the chief factor responsible for the hypertensive deaths was cardiac (2 059 cases or 79 per cent, divided into the group with myocardial insufficiency—congestive heart failure—with 1 124 cases or 43 per cent and that with coronary fatalities with 935 cases or 36 per cent) while cerebral hemorrhage caused death in 362 patients (14 per cent) and renal insufficiency in 176 cases (7 per cent) (Clawson 1941). In New England systemic hypertension is a primary or a secondary factor in at least 30 per cent of cases of heart disease. Until the last decade or two the condition had a variety of other names or was missed entirely unless blood pressure studies revealed the hypertension. It has made up a considerable percentage of cases of so-called cardiorenal disease, of so-called myocarditis, and of cardiac enlargement or failure without valvular disease and of unknown cause.

Heart disease due to pulmonary hypertension is much less common than that due to systemic hypertension but it is of considerable interest and importance and will be discussed in the next chapter. Hypertension in the portal circulation will be taken up in connection with diseases of the blood vessels in Chapter 28. Venous hypertension is discussed in Chapter 6 under Venous Blood Pressure and in Chapter 30 on Congestive Heart Failure.

**Etiology Cause** The cause of the heart disease is known—high blood pressure often abetted by some other factor especially coronary disease. The fundamental cause of the high blood pressure in the majority of cases has been however obscure and not associated with any constant clinical findings hence it has been called essential or primary. The term hyperpiesia (*hyper* over and *pieis* to press) has also been applied to it and another synonym is vascular or arterial hypertension indicating that the blood vessels are responsible.

Innumerable theories as to the cause of hypertension have been advanced since its discovery over a generation ago and some of these theories have now become facts in other words there are at least several different causes although that of the bulk of the cases (those with essential hypertension) is still (1951) to be elucidated. The association of heart disease with kidney disease was demonstrated by Bright more than a century ago (1836) but the mechanism of such association was of course unknown. Gull and Sutton (1872) pointed out the arteriolar fibrosis found in Bright's disease and in our own generation the vascular factor in hypertension has had the limelight. During the last decades however attention has been directed again to the kidneys by the pioneer work of Goldblatt (1934) who demonstrated that hypertension can be produced in animals by obstructing by a clamp the blood flow through a renal artery and by the finding of pressor substances called angiotonin and hypertensin produced by the kidney with their neutralization by other (antipressor) substances (Tigerstedt and Bergmann 1898, Houssay, Fasciolo and Taquini 1938, Page and his associates 1940, 1941, Harrison, Grollman and Williams 1940). Suffice it to say that the most acceptable and widely held theory in the light of our present knowledge is that the arterioles more or less universally throughout the body have through some direct toxic or nervous influence become irritable and pass into a state of vasoconstriction thereby increasing the resistance to the circulation of blood to which the heart responds with a resulting rise of arterial blood pressure. It is possible that the renal arterioles may play the major role in this process. At first this type of hypertension is slight and transient and may largely escape notice. Its later course is very variable the *arteriolar spasm* may subside with a spontaneous cure of the hypertension it may increase and become fixed as in the ordinary well recognized case or it may progress to an extreme and rapid degree giving rise to the so-called malignant hypertension. According to this theory there are at first no (as yet) recognizable pathologic changes arteriolar sclerosis, arterial sclerosis, renal damage (arteriosclerotic nephritis) and cardiac enlargement are secondary effects of long sustained hyperpiesia in

time the *arteriolar sclerosis itself* may be responsible for at least some of the hypertension and prevent its reduction

Hypertension is in some cases (a distinct minority) secondary to an easily discoverable cause such as gross nephritis polycystic kidneys adrenal tumor increased intracranial pressure, or congenital coarctation of the aorta or is temporarily induced by urinary obstruction congestive heart failure coronary insufficiency, pain exertion or excitement or concussion of the brain, frequently slight systolic hypertension attends thyrotoxicosis complete heart block and aortic regurgitation or marked sclerosis Under such circumstances the hypertension is not called essential or hyperpiesia In the case of hypertension of renal origin there may be an added toxic effect from renal insufficiency with or without definite uremia The surgical kidney as such is not however commonly a cause of hypertension

A number of practical classifications of hypertension have been proposed in the past a good example of which presented by Gilchrist (1941) was published in the third edition of this book A recent system, bringing this subject up to date has been presented by Page (1949) This is reproduced below It is to be observed that diastolic hypertension is far more important than systolic hypertension systolic hypertension with normal or only very slightly elevated diastolic blood pressure is much less important clinically and is apparently in the main the result of arteriosclerosis

Table 8

## CLASSIFICATION OF HYPERTENSION (PAGE)

<i>Clinical</i>	<i>Experimental</i>
<b>I Nervous Participation</b>	
Poliomyelitis of brain stem	Cerebral ischemia
Porphyria	Cushing's experiment
Increased intracranial pressure	Resection of sinus and aortic depressor nerves
Sclerosis of carotid sinus	Hypertension from audiogenic stimulus
Resection of glossopharyngeal nerve	
Emotion	
Tabs dorsalis	
<b>II Cardiovascular Participation</b>	
Coarctation of aorta	Clamping of aorta above renal vessels
Heart failure	
Arteriovenous fistula	
Arteriosclerosis	
<b>III Endocrine Participation</b>	
Hypophysis—basophil adenoma	Anterior lobectomy diminishing blood pressure
Adrenals—pheochromocytoma	Adrenaline hypertension
Cortical carcinoma	Desoxycorticosterone acetate hypertension
Cortical hyperplasia	Bilateral adrenalectomy abolishes hypertension
Thymus—carcinoma with Cushing's syndrome	Cerebrum (1951)
Placenta—associated with toxemia of pregnancy	

## IV Renal Participation

Glomerulonephritis	Antikidney serum nephritis
Obstruction to renal vessels	Mechanical constriction of renal arteries or veins
Pyelonephritis	Mechanical compression of ureters
Prostatic obstruction	Cellophane or silk perinephritis
Polycystic kidneys	
Crush syndrome	
Periarteritis nodosa	
Perinephric constriction of the parenchyma	

Hyperpiesia (essential hypertension) accounts for fully 95 per cent of the cases of hypertensive heart disease and obvious renal disease for most of the rest. About two thirds of the cases of established diastolic hypertension show cardiac enlargement on examination. Still others have lesser grades of enlargement too slight to discover clinically. Hypertension, whether or not of the essential type, may be too slight or recent in onset to cause any cardiac hypertrophy at all.

**Age.** Hypertensive heart disease like hypertension itself (especially hyperpiesia) is commonest in middle age and after. Signs of it appear on the average ten years after the onset of sustained hypertension of an important degree, except when there are complications (valvular disease or coronary disease) to make its effect more quickly evident. Of a series of 708 cases of hypertensive heart disease 62 per cent were in the sixth and seventh decades (29 per cent in the sixth and 33 per cent in the seventh), 17 per cent were over seventy years of age, 16 per cent were in the fifth decade, 4 per cent in the fourth, 1 per cent in the third, and 0.5 per cent were below twenty years old; thus only 21 per cent of the cases were less than fifty years of age (White and Jones, 1928). In a more recent series of 1,249 cases 68 per cent were between fifty and seventy (White, 1936). The youngest case of essential hypertension with autopsy on record that I know about has been reported by Gaussig and Remsen (1935): a colored boy two years old.

**Sex.** There is not much difference between the sexes in the incidence of hypertensive heart disease. In White and Jones' series of 708 cases 55 per cent were female and 45 per cent male. In the more recent series of 1,249 cases from my own practice 51 per cent were male and 49 per cent female. Hypertension itself, on the other hand, is far more common in females than in males, by a ratio of about 2 to 1. Yet it is true that it is much more serious in the male. Blackford and Wilkinson (1932) found the mortality rate after ten years twice greater in men and among 50 consecutive cases of my own with serious cardiovascular sequelae of hypertension selected for sympathectomy 38 were male and 12 were female (White et al., 1950).

**Heredity.** Of all known etiologic factors in the production of hypertension and so of hypertensive heart disease, heredity ranks as of the greatest importance. Frequently many members of one family in the course of a few

generations have either shown essential hypertension or have had troubles coming from such a condition. The way in which heredity acts is obscure but we do know of its great significance.

*Race and climate* are factors of some importance. Hypertension is less marked in tropical and semitropical climates and it is said to be uncommon in certain nationalities like the Chinese when in their own country, whether this is because of race or of other factors like tempo of life or diet we do not know. It is especially common among the Negroes in the United States apparently twice as common as in the white population for reasons unknown. It is said that in Africa on the other hand hypertension is rare among the Negroes who tend however to succumb to other ills especially tropical diseases at relatively early ages before the years when essential hypertension is at its peak in America. We need much international research on this problem.

*Diet and obesity* Overeating and obesity frequently are associated with hypertension and hypertensive heart disease but the relationship is a very constant one on both sides. A high protein diet was once blamed for the production of hypertension but this has been refuted, on the other hand a diet overrich in food value in general may be of importance. During the war in Holland over a period of starvation from September 1944 to May 1945 there was a frequent lowering of blood pressure associated with weight loss especially in hypertensive patients (Lups and Francke 1947). There are problems here in need of solution.

*Nervous and physical strain* It is believed by many observers that a life of high nervous tension favors the production of hyperpiesia or at least its aggravation the latter is the more likely. Physical strain and constant laborious work although sometimes blamed as aggravating factors have been largely exonerated in late years indeed it seems possible that physical exercise in moderation at least may protect against hyperpiesia.

*Endocrine disturbances* are frequently attended by hypertension but rarely by marked hypertension these disturbances are especially associated with the ovarian function (for example, menopause and oophorectomy), with thyrotoxicosis and with adrenal or pituitary tumors. In the case of thyroid or adrenal or pituitary oversecretion surgical removal of a large part of the thyroid gland or of an adrenal or pituitary tumor may result in a return of blood pressure to normal. The discovery that an excess of basophilic cells is present in the posterior lobe of the pituitary gland (hypophysis) in certain cases of pituitary adenoma with hypertension and of eclampsia (Cushing 1932) suggested that hyperpiesia might have its basis therein but this suggestion has not been confirmed only a small minority of cases are to be so explained.

Infections and poisons have not been shown to have any close connection with the pathogenesis of hyperpiesia this statement includes lead long blamed for hypertension.

*Pathology* The pathology of hypertensive heart disease is as a rule very

simple Both cardiac and vascular abnormalities in chronic hypertension are primarily but natural responses of muscle to increased work. Hypertrophy of the individual muscle fibers of the left ventricle is always present sometimes to such a degree that the heart is greatly enlarged (Figure 95). A heart weight of about 500 gm (normal = 200 to 350 gm) is common and in rare cases this may be increased to 750 or even to 1 000 gm. With the development of failure

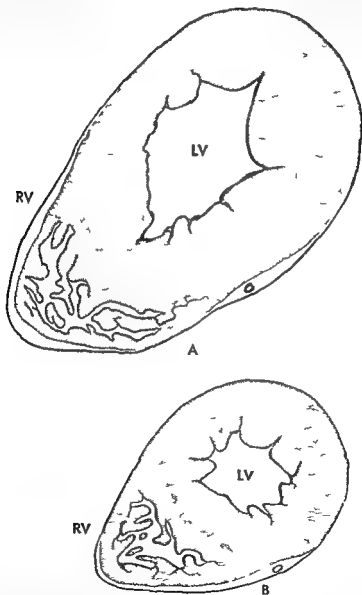


FIG 95 Drawings showing cross sections (actual size) of (A) an enlarged hypertensive heart and of (B) a normal heart at a level two thirds of the distance from base to apex of the ventricles. LV = left ventricle RV = right ventricle

dilatation appears changing the appearance of left ventricular hypertrophy from concentric to eccentric. Such left ventricular dilatation is followed by dilatation of the mitral valve ring functional mitral regurgitation dilatation of the left atrium and enlargement of the right ventricle and atrium too if the left ventricular failure lasts long enough. It has been suggested that the primary hypertrophy of the heart muscle begins only after it has been strained or traumatized and somewhat dilated by the early efforts to overcome the effect of the arteriolar constriction. Since with systemic hypertension the pulmonary arterial blood pressure usually remains normal (until the left ventricle fails) the right ventricle is unaffected early in the disease. Eventually after the left ventricle has begun to fail the pulmonary blood pressure rises and the right ventricle in its turn is subjected to considerable strain and begins to enlarge as a matter of fact the commonest cause of right ventricular enlargement is failure of the left ventricle secondary to systemic hypertension.

There is no actual myocarditis or myocardial degeneration in most cases of uncomplicated hypertensive heart disease even in massive hearts with marked congestive failure, some myocardial scarring (fibrosis usually in small areas) is however not uncommon even in the absence of coronary disease (Levine V 1934). Endocarditis and pericarditis do not occur primarily in this type of heart disease although endocardial sclerosis most marked in the left atrium which first bears the brunt of left ventricular failure was found in all of a series of 27 hypertensive hearts (Levine V 1934).

The aorta normal at first becomes dilated in older and chronic cases but never to the degree observed in advanced syphilitic aortitis. Some of the dilatation seen by roentgen ray examination is not found post mortem since it is temporary depending on the intra aortic hydrodynamic state. The vascular dilatation may extend a little into the aortic branches especially into the innominate and carotid arteries. Rarely the aortic media may split to cause a dissecting aneurysm when hypertension is complicated by an abnormally weak spot in the aortic wall.

Thickening of the arteries and arterioles throughout the body is a common finding in chronic hypertension and in all probability is a vascular response to the hypertension. Arteriolar sclerosis and obliteration may complicate the picture. Hypertension without arteriosclerosis and arteriosclerosis without hypertension are frequent findings but the two combined are as frequent as either condition alone. Renal arteriolar sclerosis is preponderant and is universally found in the higher grades of hypertension although not as a rule at the onset of the disease.

**Symptoms.** There are no symptoms of hypertensive heart disease until complications arise the condition is often discovered incidentally in the course of routine examination. Usually the person feels perfectly well and is simply annoyed by the discovery of the high blood pressure or of the enlargement of the heart. Occasionally however, there are headaches and a coincident neurocirculatory asthenia with its various symptoms including palpitation heartache and dyspnea. These symptoms are frequently erroneously attributed

by patient and doctor alike either to the high blood pressure or to heart disease although it is true that a person subject to neurocirculatory asthenia will have more symptoms if the blood pressure is high and the heart is enlarged than when the blood pressure and heart are normal and in some cases headache is part of a disturbance of the cerebral circulation incident to the hypertension (hypertensive encephalopathy). A neurosis is common with hypertension and hypertensive heart disease usually the result of fear of the high blood pressure. When true symptoms of hypertensive heart disease do arise they are most commonly those of cardiac insufficiency which may increase to well marked congestive failure resulting from the myocardial strain and fatigue which involve primarily the left ventricle.

Dyspnea on exertion is usually the first authentic symptom tending to increase in degree unless checked by the institution of proper treatment. With marked failure dyspnea may become constant and prevent a recumbent position (orthopnea). Or there may be sudden attacks of acute failure of the left ventricle occurring during sleep at night or less often in the daytime after exertion or excitement with engorgement of the pulmonary circulation, pulmonary edema and sometimes the setting off of asthmatic respiration. Such an attack of wheezing is called cardiac asthma and is not an infrequent syndrome in the case of the failing hypertensive heart; it varies considerably in duration but lasts usually about an hour.

Pain is less common in hypertensive heart disease than is dyspnea. It takes two forms: sometimes a precordial ache due to an associated neurocirculatory asthenia (or effort syndrome) aggravated by the cardiac enlargement and sometimes angina pectoris from an associated coronary disease or syphilitic aortitis. Angina pectoris however though common in hypertension because of the age incidence is not so characteristic as is dyspnea for the hypertensive strain results in an inability of the left ventricle to maintain the general circulation more often than in the inability of the coronary circulation to supply the heart muscle with blood unless we accept the possible theory that some hypertension especially if it involves the diastolic pressure may result from the need of greater force to maintain an adequate coronary circulation. The prolonged pain of coronary occlusion occasionally complicates hypertensive heart disease.

Palpitation is common in hypertension with or without heart disease especially in sensitive persons due either to the consciousness of the forceful heart action with normal rhythm particularly on exertion or excitement or to the occurrence of unimportant premature beats, paroxysms of tachycardia or atrial fibrillation. These various disturbances of rhythm are common in hypertensive heart disease but they are not characteristic. Of the group of 708 cases of hypertensive heart disease of White and Jones (1928) 92 (or 13 per cent) had atrial fibrillation (14 of these were paroxysmal in type); paroxysmal tachycardia was noted in 11 patients (1.5 per cent); atrial flutter in 2 (0.3 per cent); and atrioventricular block in 13 (1.8 per cent)—the last named being due to an associated coronary disease and not to the hypertension.



Other symptoms frequently found in essential or in nephritic hypertension with or without heart disease are familiar tinnitus weakness nosebleeds or other hemorrhages symptoms of cerebral accident (aphasia and paralysis) whether transient (hypertensive cerebral vascular crises or minute lesions) or more or less lasting (cerebral hemorrhage or thrombosis), and symptoms of renal insufficiency (drowsiness coma and vomiting from uremia) The term hypertensive encephalopathy is used to cover all the various cerebral vascular disturbances due to hypertension from slight dizziness to extensive apoplexy, in frequency as a serious complication it ranks below the cardiac effects but above the renal

**Signs** The only constant sign of hypertensive heart disease is cardiac enlargement due mainly to left ventricular hypertrophy The hypertension itself responsible for this enlargement may have subsided at the time of examination though some trace of it usually exists If there is no increase in heart size even though hypertension is present we cannot label the condition hypertensive heart disease although as after rheumatic fever we may speak of potential heart disease In the early stages of hyperpiesia and even in more chronic cases when the blood pressure is but slightly elevated the heart may be able to stand the strain without increase in size but a normal heart size is rare if it exists at all, with markedly high blood pressure of long duration Finally it is to be observed that the cardiac enlargement of hypertensive heart disease may be present in slight degree to be discovered only at postmortem examination not being sufficient to give evidence during life An addition to the heart weight of 25 50 or perhaps even 100 gm in the absence of dilatation can probably not be detected clinically even by careful roentgen ray examination unless there are frequent serial records Hence the clinical statistical report that about two thirds of the cases with hypertension eventually show cardiac enlargement undoubtedly falls somewhat short of the actual figure as indicated by the statistical study of Murphy and his associates (1932) who found that in a series of 375 cases of essential (primary) hypertension examined post mortem the heart weights were 400 gm or above in 81.87 per cent (normal upper limit of heart weight = 350 gm in the male and 300 gm in the female)

In systemic hypertension with or without heart disease the aortic second heart sound is usually accentuated sometimes to a striking degree When the left ventricle begins to fail the pulmonary second heart sound increases in intensity in its turn as the pulmonary blood pressure rises and finally the pulmonary second sound equals or quite commonly exceeds the aortic second sound in intensity even though the latter continues to be louder than normal The changing relationships of the intensities of these two sounds is of great interest and importance affording a valuable but much neglected clue to the degree of sufficiency of the left ventricle

With increasing size of heart and the development of dilatation of left ventricle and aorta under the strain of the hypertension apical and aortic systolic murmurs appear and are common in the more advanced cases the former due to functional mitral insufficiency and the latter chiefly to the aortic dilata

tion In still more advanced cases especially when arteriosclerosis complicates the picture the aortic valve ring itself may stretch either temporarily under the head of pressure or more or less permanently to give rise to an aortic diastolic murmur (aortic regurgitation usually functional) In a series of 500 cases of hypertension (Paulin 1927) a mitral systolic murmur was noted in 26 per cent an aortic systolic murmur in 6 per cent and an aortic diastolic murmur in  $2\frac{1}{2}$  per cent in another series of 200 consecutive autopsied cases of hypertensive heart disease with normal aortic valves reported by Garvin (1940) a diastolic murmur had been heard at the base of the heart apparently aortic in origin in 14 cases resulting in a frank error in etiologic diagnosis in four instances

The aortic dilatation due to hypertension may not be marked enough to be found on physical examination but it is generally easily seen fluoroscopically It consists of a general enlargement of the whole thoracic aorta The ascending aorta is not as a rule so dilated as in syphilitic aortitis and there are no aneurysmal pouches A point of especial interest concerning the aortic dilatation in hypertension and incidentally also in cases of aortic regurgitation is that the dilatation is at first functional or dynamic at that stage failing to appear at autopsy even though very evident by roentgen ray examination during life

A common sign resulting from two factors the vascular dilatation and the pushing up of the great vessels by the cardiac enlargement and the high diaphragm so often found in obese persons especially women with hypertension is a prominence with pulsation of the innominate artery and the origin of the carotid artery at the base of the right side of the neck just above the inner end of the clavicle this is so marked sometimes that it resembles a small aneurysm

When congestive heart failure arrhythmias or other complications arise the usual signs of such troubles appear and the heart tends in the case of failure to become very large with increasing dilatation The appearance of gallop rhythm of the protodiastolic type is a frequent and serious sign of cardiac dilatation and failure in hypertensive heart disease The relative frequency of arrhythmias in hypertensive heart disease has been noted above their incidence is less in hypertension as a whole One of the most important disorders of heart action—pulsus alternans (see Chapter 8)—is relatively common in the case of the failing hypertensive heart and is much more common than generally thought it is most readily detected during the course of blood pressure measurement and it usually means that death is at best but a few years off (see Chapter 30)

One of the most helpful and constant signs of chronic hypertension and therefore usually associated with hypertensive heart disease is sclerosis of the arteries in the eye grounds (fundus oculorum) this is far more constant than in the case of general or coronary arteriosclerosis or of nephritis In slight to moderate grades of hypertension there may be little change in the fundi from none at all to silver wire appearance of the arterioles with nicking of the veins where the arteries cross them but in advanced or serious cases

hemorrhages appear in the eye grounds and areas of degeneration are found (see Figure 9 page 54) Moreover an early finding of marked retinal changes suggests that the type of hypertension is "malignant" with a bad prognosis (even though the kidneys may be relatively normal at the time)

Signs of serious involvement of the brain may appear in the course of hypertensive heart disease such as paralyses and abnormal reflexes or there may develop evidence of involvement of the kidneys albuminuria many casts in the urinary sediment oliguria low specific gravity of urine lowered renal function and nitrogen retention in the blood but it is to be remembered that in congestive heart failure due to hypertension albuminuria casts and other urinary abnormalities may be caused by congestion without nephritis and that a relatively unimportant vascular nephritis may develop secondarily due to the hypertension with such signs as those noted above and without congestive failure

The blood pressure in hypertensive heart disease generally remains high but sometimes either because of spontaneous remission or because of heart failure or general vasomotor collapse and in some cases evidently aided by treatment it may fall to average normal or nearly normal levels leaving obscure the cause of the cardiac enlargement and failure unless knowledge exists of the previous hypertension The diastolic pressure in such cases may be maintained at a somewhat high level (100 to 110 mm for example) even though the systolic pressure has fallen to 150 mm or below this relatively high diastolic pressure and low pulse pressure may in some cases reveal the previous hypertension In fact as already noted in the discussion of the clinical classification of hypertension the systolic level of the blood pressure is far less important than the diastolic so far as strain on heart arteries and kidneys is concerned a rise of a few millimeters of mercury of diastolic pressure is a great deal more serious than several times that rise of systolic pressure A full pulse pressure with elevated systolic pressure and normal diastolic is common in advanced sclerosis of the larger arteries (with loss of elasticity) and relatively normal arteriolar circulation (that is, without essential hypertension)

It is not known how frequently cardiac enlargement is the result of an old hyperpiesia in the absence of hypertension at the time of examination and without evidence of valvular disease serious coronary disease pulmonary fibrosis or pericardial disease Some writers believe that it is always or almost always so produced This is a possibility but by no means a certainty Some causes for enlargement of the heart exist which are not yet clear while others previously unrecognized have in recent years been brought to light More study of this problem is needed

The systolic pressure in established hypertension varies from 150 to over 300 mm of mercury it is usually about 200 The diastolic pressure varies from 90 to 180 but is usually 110 to 120 The pressure readings (especially the systolic) vary greatly among different individuals and on different occasions in the same individual Repeated measurements must often be made before the customary basal blood pressure levels for a given patient are dis-

covered uninfluenced by excitement exertion or fatigue. It has been found as would be expected that the blood pressure levels recorded by the patient himself or herself at home tend to be distinctly lower than they are in the clinic or doctor's office (Ayman and Goldshine 1941). It must be remembered however that neither record is truly representative and that hypertension until fixed is likely to go through wide swings from day to day or hour to hour. The lability of the pressure is of some importance in prognosis and treatment too: the more favorable cases tending more often to show pressures close to normal. To test the degree of the lability various procedures have been introduced including especially (1) the *measurement of the blood pressure at frequent intervals* day and night (2) the *cold pressor test* consisting of immersing one hand in ice cold water at 40° F for 30 to 60 seconds which will cause a mean rise of over 30 mm of mercury in systolic pressure and of over 25 mm in diastolic pressure in hypertensive individuals or somewhat less in hyperreactors (who may some day become hypertensive) and much less in normal nonhypertensive persons (Hines and Brown 1936) (3) the *sedation test* consisting of the effect of extreme sedation by the ingestion of 3 gr of Sodium Amytal every hour for three doses the blood pressure dropping to normal in the early or mild and labile cases and (4) the *postural test* the diastolic pressure rising in hypertensive cases 15 to 30 mm with less change in the systolic level and hence a drop in pulse pressure readings on assuming the erect position.

A very high diastolic pressure is a bad sign and a constant finding of such a pressure over 130 mm of mercury means that without special treatment but a few months or years of life remain. The auscultatory gap found by the auscultatory method of sphygmomanometry (discussed in Chapter 6) and *pulsus alternans* (to be discussed in Chapter 30) are both common in hypertension and appear during blood pressure studies. The blood pressure should be measured in spite of the presence of atrial fibrillation: an approximate figure so obtained is generally sufficiently accurate. When hypertensive crises occur due to adrenal medullary tumors (*pheochromocytomata*) or to vasomotor (arteriolar constriction) storms in the course of chronic hypertension sometimes with serious effects such as apoplexy the blood pressure may suddenly rise 50 to 100 or more millimeters systolic and half that diastolic.

Special tests for a *pheochromocytoma* have been developed consisting of sharp increase of blood pressure on administration of histamine, Mecholyl or tetraethylammonium chloride; no reaction to epinephrine and reduction of blood pressure on intravenous injection of benzodioxane. The more established tests are those with histamine (Roth and Kvale 1945) and benzodioxane (Goldenberg, Snyder, Aranow 1947). The former test consists of determining the basal blood pressure and pulse records after recumbency for  $\frac{1}{2}$  to 1 hour then every minute for 15 minutes after the intravenous injection of 0.025 to 0.05 mg of histamine (0.25 to 0.5 cc of 0.01 per cent solution in normal saline). A positive reaction is shown by a sharp rise of blood pressure of 100 mm or more in the presence of a *pheochromocytoma* in contrast

to a much slighter rise in a case of essential hypertension. The severity of this reaction has resulted generally (except when the blood pressure is not much elevated to start with) in replacement by the benzodioxane test, which consists of the intravenous injection in 2 minutes via a normal saline drip (in operation for 20 to 30 minutes before the test) of 0.25 mg per kilogram body weight in 1 per cent solution of piperidymethyl benzodioxane (933 F), an adrenolytic or epinephrine antagonistic substance. A positive reaction consists of a considerable fall in both systolic and diastolic pressures in the course of a few minutes. Less satisfactory testing for a pheochromocytoma includes perirenal air insufflation which can be difficult and dangerous and nondiagnostic in some cases when the tumor is situated not at the adrenal gland but elsewhere along the sympathetic chain as it sometimes is.

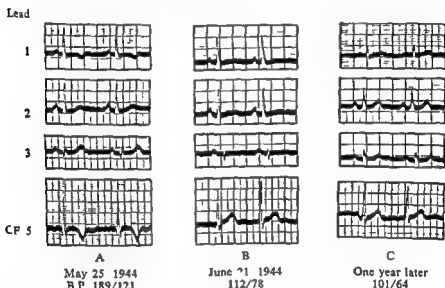
Roentgen ray examination in hypertensive heart disease shows cardiac enlargement chiefly of left ventricular type (Figure 96 illustration below) and



FIG 96 Roentgenogram showing a moderately enlarged hypertensive heart with prominence of the left ventricle. The arc of the descending aorta is well seen above the heart shadow because of its increased density (arteriosclerosis). The pulmonary artery is not enlarged; there has been no pulmonary vascular congestion.

general dilatation of the aorta with prominence of both ascending and descending portions in the thorax. Later in the disease when left ventricular failure begins greater cardiac enlargement is found due to dilatation and to involvement of the right side of the heart and of the left atrium. Then the lung hulus shadows and the pulmonary artery shadow tend also to be prominent in keeping with the newly developed hypertension in the pulmonary circulation.

Electrocardiography often shows no abnormality in hypertensive heart disease but in the majority of chronic cases there is characteristic hypertensive pattern (Figure 97A) consisting of lowering to inversion of the *T* waves in Lead I and in the leads over the left ventricle ( $V_4$ ,  $V_5$  and  $V_6$ ) and of in



10 97 Reversal of the hypertensive electrocardiographic pattern after lumbodorsal sympathectomy. Male age 39. Lumbodorsal sympathectomy right side May 31 1944 left side June 9 1944.

creased amplitude of the *R* waves in these same leads there is frequently also left axis deviation as found in the classical bipolar limb leads although a horizontal heart position commonly found in hypertensive patients is more responsible for such axis deviation than is left ventricular enlargement. It is likely that dilatation in addition to hypertrophy of the left ventricle is responsible for this abnormality of the electrocardiogram as borne out by the return to a more normal record in some cases when the hypertension and left ventricular strain therefrom are relieved by splanchnic resection (Figure 98 page 487). Arrhythmias are not the rule but when they appear they are well shown in the electrocardiogram.

**Course and prognosis.** Hypertensive heart disease tends to be a progressive condition leading sometimes rapidly but usually slowly to congestive heart failure in the course of 10 to 20 years. The condition begins as a rule in-

sidiously and very gradually in middle life at about forty to fifty years of age and is often discovered in the course of routine blood pressure or cardiac examination (for life insurance for example) When it begins in youth it is more serious when it begins in old age it is not so serious unless coronary disease or cerebral arteriosclerosis complicates the condition Sometimes at first there are merely waves or periods of hypertension with normal pressure between Transient or paroxysmal hypertension may however in the course of time do as much harm to some patients as sustained hypertension in the usual run of cases Even when the hypertension becomes fixed there tend to be waves or periods of considerable increase above the average level for example a systolic pressure of 180 mm may rise to 240 for a few hours at a time on excitement fatigue or from unknown cause There may be a mild and temporary increase of blood pressure or an exacerbation of a pre-existing hypertension at the time of the menopause

The term *malignant hypertension* has been introduced to designate an extreme grade of hypertension with a rapidly fatal course (months to a year or two) Actually however it includes a variety of severe cases those that are marked and serious from the very beginning (usually young adults), those approaching the end of a long hypertensive course and those who after some years of a fairly benign hypertension take a rather abrupt turn for the worse The chief characteristics of malignant hypertension are the high diastolic blood pressure (130 to 140 mm or over) the very abnormal eye grounds and the bad prognosis and rapid course

Although heart failure is the most common of the end results of hypertension cerebral hemorrhage is also frequent angina pectoris and coronary thrombosis are next in order and renal insufficiency is least common In a series of 410 cases of primary or essential hypertension examined post mortem (Bell and Clawson 1928) congestive heart failure was found in 187 cases (44½ per cent) cerebral hemorrhage or thrombosis in 81 cases (19 per cent) coronary heart disease in 67 (16 per cent) renal insufficiency in 36 (8½ per cent) and miscellaneous conditions in 49 (12 per cent) In a later series (1941) of 2 597 hypertensive patients who succumbed to cardiovascular disease Clawson found that death was caused by myocardial insufficiency in 43.3 per cent by coronary heart disease in 36 per cent by cerebral hemorrhage in 13.9 per cent and by renal insufficiency in 6.8 per cent In the series of 375 hypertensive cases studied by Murphy and his associates (1932) heart failure (mostly congestive but including coronary) caused 50 per cent of the deaths, infections 14.2 per cent apoplexy 13.4 per cent and renal failure 10.4 per cent Fahr (1935) put the percentage of deaths in hypertensive cases due to congestive heart failure at 55

Serious prognostic signs are very high diastolic blood pressure (over 130 mm) marked changes in the eye grounds pulsus alternans gallop rhythm and paroxysmal dyspnea or cardiac asthma A serious prognosis should not be given on the finding of slight or moderate hypertension or slight cardiac

enlargement alone. Much cardiac enlargement or sustained hypertension of very high degree warrants a grave prognosis.

On the other hand, within the last decade a change has taken place in the course and probable prognosis of some of the cases of hypertension, even of high grade with hypertensive heart disease, as the result of the more complete splanchnic sympathectomy carried out by Smithwick (1940) and observations made by myself on his cases (1942-1951). Occasionally striking results have occurred with relief not only of the hypertension, eye ground changes and symptoms but also of the physical and electrocardiographic evidences of the heart strain, such as gallop rhythm, pulsus alternans and *T* wave abnormalities. In at least a few of these cases the hypertensive heart disease should be regarded like the thyrotoxic hearts and some instances of acute rheumatism as a reversible process in its acute or subacute stage. The strict application of low sodium and of Kempner's rice diets has also reversed or retarded the hypertensive process in some, though relatively fewer cases.

**Complications.** The most important complications of hypertensive heart disease and their relative frequency have been noted above: congestive heart failure, apoplexy, angina pectoris, coronary thrombosis and nephritis with uremia. Acute infections are common and may end the story, as may also pulmonary embolism from phlebothrombosis in the leg, especially after congestive heart failure has set in. Arteriosclerosis is almost universally found in older patients with hypertension but, although undoubtedly favored by the strain of the high blood pressure, it is not by any means a constant finding. Types of heart disease other than that due to coronary sclerosis may complicate the enlargement and weakness from hypertension. Syphilitic aortitis, thyrotoxicosis and rheumatic heart disease are not infrequent complications. Hypertension is often found with aortic regurgitation and with mitral disease with or without much stenosis, and it is not rare even with aortic stenosis. Finally, nervousness and neurocirculatory asthenia are common complications of hypertensive heart disease and frequently exaggerate the seriousness of the symptoms and of the condition itself.

**Treatment.** The treatment of hypertensive heart disease resolves itself into three parts, consisting of (1) the therapy of cardiac complications, (2) the therapy of the underlying hypertension and (3) preventive measures to protect the damaged heart.

(1) The treatment of the cardiac complications, such as congestive failure, cardiac asthma, angina pectoris, coronary thrombosis and atrial fibrillation, will be discussed in later chapters of this book, mainly in Part IV. The presence of hypertension does not in any way contraindicate the usual measures, for example, the use of digitalis for failure or for atrial fibrillation, of nitrites for angina pectoris, of morphine for coronary thrombosis and cardiac asthma, and of quinidine for atrial fibrillation. It need hardly be added that the most important measure of all, not in the emergency but when the emergency is over, is an attempt if it seems feasible by medical or surgical measures



(outlined below) even in the absence of specific therapy to reduce the main factor of strain namely the hypertension

(2) The treatment of the hypertension itself continues to be a difficult task in the present state of our knowledge but important studies in progress offer much hope for the future

**Drugs** Many measures especially medicinal to reduce high blood pressure have been suggested and tried sometimes with slight temporary success sometimes with toxic effects sometimes though rarely with prolonged benefit these include such drugs as the nitrites bismuth subnitrate benzyl benzoate atropine calcium chloride potassium iodide bromides parathyroid preparations theobromine theophylline ethylene diamine (called also aminophylline, and formerly Euphyllin or Metaphyllin), theobromine sodiosalicylate (Diuretin) theobromine sodium acetate (Thesodate) and other diuretics cucurbitin (from watermelon seeds) papaverine mistletoe (*intraut de gui*) sunflower seeds garlic yohimbine liver extract ovarian extract testosterone chloral hydrate and other sedatives or hypnotics like phenobarbital (Sodium Luminal) cathartics sulphur and the sulphocyanates (thiocyanates) of sodium or potassium In one series of 70 patients with established essential hypertension (Evans and Loughnan 1939) the effects of 33 different preparations and of a placebo on the blood pressure and on the symptoms were observed None produced a satisfactory hypotensive effect Symptomatic improvement greater than that resulting from the placebo followed the use of only six of the drugs namely bismuth subnitrate iodine and iodide bromide Sodium Luminal (phenobarbital) Theominal (theobromine and phenobarbital) and potassium thiocyanate The sedative drugs seemed to have value in temporarily relieving nervous symptoms when these were prominent and since it is now well established that heavy sedation (e.g., Sodium Amytal 0.2 gm 3 gr every hour for three doses) frequently reduces hypertensive blood pressure readings markedly even to normal there is an additional good reason therein for the therapeutic use of sedative drugs

There has been in recent years a revival of the use of the thiocyanates (sulphocyanates) and of *veratrum viride* and various of its derivatives which appear to be more effective in reducing the blood pressure and in relieving symptoms in hypertensive patients than do other drugs However their effect has been often disappointing and sometimes seriously toxic They should be used under close observation best controlled in the case of the thiocyanates by frequent measurements of the concentration of the drug in the blood itself (preferably kept at 6 to 12 mg per 100 cc blood)

*Veratrum viride* has been in use for many years in the treatment of eclampsia frequently with considerable reduction of blood pressure but complicated by toxic symptoms The drug under various trade names has been in use also for some time in the treatment of essential hypertension with similar results An analysis of its effects has been published by Freis and Stanton (1948) Only recently have satisfactory extracts been made from *veratrum* in the form of purified alkaloids One of these called protoveratrine from *Vera*

trum album has given much promise as indicated by its uniform reduction of both systolic and diastolic pressures for several hours at a time without serious toxic symptoms in hypertensive animals and man when given parenterally (Meilman and Kraye 1949). More recently still protoveratrine has been given orally to ambulatory patients with beneficial effects over periods of weeks and months but the dosage has to be very carefully regulated for each individual to obtain the best hypotensive effect with the least toxic result. The dosage parenterally varies from 0.25 to 1.0 mg every 6 hours and orally from 0.5 to 2.0 mg every 8 hours. This drug has proved to be especially useful in patients who are too old or otherwise unsuitable for lambdodorsal sympathectomy. Whether or not protoveratrine or some other even more effective medicament can actually replace operative treatment it is too early to say. It should be added that the heart rate as well as the blood pressure is considerably reduced by veratrum derivatives even down to 40 per minute.

Other derivatives from veratrum viride that have been used somewhat helpfully in cases of hypertension are Vertavis (15 to 30 Crow units daily) and especially Veriloid which can be given in the dosage of 2 to 3 mg orally every 6 hours (Wilkins Stanton and Freis 1949, Connor Emlet and Grimson 1950). It may be added that atropine should be available to counteract toxic effects from any veratrum preparation.

Potassium thiocyanate is conveniently given in the form of a 4 to 8 per cent solution in peppermint water or in a simple syrup such as that of sarsaparilla and in the dosage of one teaspoonful (4 cc) containing 0.16 to 0.32 gm ( $2\frac{1}{2}$  to 5 gr) three times a day (total of 0.5 to 1.0 gm or  $7\frac{1}{2}$  to 15 gr) the dosage varies as circumstances warrant. In one of the largest groups of cases reported that of 246 by Barker and his associates (1941) symptoms were relieved and blood pressure was reduced in 47.5 per cent in the course of two to four weeks. In another series of 50 patients subjective improvement was definite in 63 per cent fair in 20 per cent and disappointing in 17 per cent six showed toxic effects the blood pressure of every patient was somewhat reduced and objective results were considered satisfactory in 78 per cent fair in 16 per cent and poor in 6 per cent the average systolic pressure dropped from 197 mm before treatment to 156 mm with treatment and the average diastolic pressure dropped from 115 to 94 the average maintenance dosage of 5 gr varied from three to twenty-one (average nine) times per week. In another group of 20 patients with pronounced arterial hypertension (Blaney Geiger and Ernst 1941) to whom potassium thiocyanate was given after a control period on placebos one half of the total number apparently responded with a complete or partial remission of their hypertension eight of the 16 patients with symptoms felt better during the therapy a few felt worse. In still another group 120 hypertensive patients were treated (Caviness and associates 1941) with results recorded as good in 68.9 per cent (reduction of more than 15 per cent in both systolic and diastolic pressures) fair in 11.5 per cent and poor in 19.6 per cent. Other authors however have emphasized the toxic effect of the drug (Wald Lindberg and

Barker 1939, Robinson and O Hare 1939), the last named authors reported toxic symptoms in 29 (38 per cent) of their 75 patients less serious in 23 of them (nausea, weakness dermatitis purpura and a decrease in libido) and more serious in the other 6 (dermatitis exfoliativa congestive heart failure cerebral thrombosis angina pectoris and psychoses), but at the same time they believed that there was decided value in the therapy when carefully controlled (maximum drops in blood pressure of over 100 mm systolic and 35 mm diastolic were observed in 3 cases, average drops of 40 mm systolic and 20 mm diastolic in 63 per cent of the patients and relief of hypertensive headaches in 18 out of 20 cases)

Rogers and Palmer (1947) compared the use of thiocyanate therapy in hypertension to sympathectomy by Smithwick's operation, they found that only about one fifth of 100 patients showed any considerable fall in blood pressure from the effect of the drug and that such falls required continuous therapy for their maintenance and were not at all comparable to the drop in pressure obtained in favorable cases by splanchnic resection once in a while however the drug produced brilliant results in the relief of headache

Recent papers on the administration of the thiocyanates emphasize a general dissatisfaction with their use (Ruskin and McKinley 1947) and their greater value in the absence of organic changes (Alstad 1949)

Other drugs more recently introduced with definite hypotensive but generally disappointing effects include tetraethylammonium chloride dihydroergocornine derived from ergot Dibenamine and Driscoll Still other medicaments recently recommended but unconfirmed include procaine HCl in honey thyroid extract and Rauwolfia serpentina Rutin a flavone rhamnogalactoside extracted from wheat germ has been used to reduce the hazard of hemorrhage from capillary fragility in essential hypertension but there has been considerable doubt as to its clinical value

Most recently hexamethonium salts have been tried for hypertension (Smirk 1951, Locket et al, 1951 George W Pickering personal communication 1951) it appears to be effective if given intramuscularly 3 or 4 times a day at increasing dosage beginning with 15 mg

**Diet** Dietary restrictions have been tried particularly the limitation of the total caloric value of the diet of protein food and of common salt Reduction of weight has been carried out with some benefit in a good many obese patients reference has already been made earlier in this chapter (page 468) to the hypotensive effect of starvation with resulting loss of weight.

Two special diets are in common use today in the treatment of hypertension because of their success in some though in the minority of cases One of them introduced years ago emphasized the need of restriction of sodium chloride (Allen 1920) and has been resumed and studied in recent years with variable success It has been shown that it is the sodium content of the diet that is important as it is in the case of the dietary treatment of congestive heart failure in fact it is the hypertensive patient with congestion threatened or present who receives the most benefit Just how on occasion the sodium

striction acts on hypertension has not yet been elucidated its relationship to adrenal function among other mechanisms has been indicated

The other diet which in recent years has been much utilized in the treatment of hypertension is the rice diet introduced by Kempner (1944) In the first place this diet has about as low a sodium content as it is possible to give (less than 0.5 gm) secondly it is very low also in protein (about 20 gm daily) and thirdly it contains very little fat (about 5 gm daily) It consists of rice fruit and sugar with no other food during the first six weeks or more of treatment but later is liberalized according to circumstances The explanation of its success is still unclear but in those persons who are faithful to it (a minority of cases) there is an improvement of abnormal eye grounds electrocardiogram and heart size and a definite reduction in blood pressure both systolic and diastolic in more than half (the exact percentage has not yet been determined) whether or not there has been a loss of weight There need be no weight loss since the diet contains at least 2 000 calories As in the case of the low sodium diet so here too it is the somewhat congested hypertensive patient who seems to receive the most benefit and also some cases of renal involvement for whom as a matter of fact the diet was first introduced

It should be emphasized that the conscientious following of this 'rice diet' has been helpful in the case of many hypertensive patients including some not improved by other therapeutic measures medical or surgical including sympathectomy also that it can be added helpfully to other treatment not sufficiently effective per se

Much study remains to be done on the effect of diets on hypertension and it is to be observed also that on occasion there may develop from either of the diets noted above a serious sodium lack requiring emergency treatment

**Other medical measures** Measures of physical therapy have been advocated rest physical and mental baths of all kinds venesection electrotherapy (high frequency diathermy) and roentgen ray irradiation of the pituitary and adrenal glands Psychotherapy has been used both consciously and unconsciously along with attempt to adjust or to remove strain of professional or business life of family affairs and of social activities Often these measures have been combined in various ways and degrees particularly at special health resorts or spas and often by the family doctor or specialist at home

The imposing list of remedies and their advocacy by so many different persons reveal their very weakness we have not yet a real cure or a specific treatment for hypertension except on the one hand surgical removal of certain unilaterally diseased or deformed kidneys and pheochromocytomata in rare cases and on the other hand thoracolumbar (lumbodorsal) sympathectomy in suitable cases Whether to match the numerous causes of hypertension we may have to develop a variety of cures or whether a single drug or chemical or other measure will neutralize hypertension in the majority of cases no matter what the original cause we do not yet know

Rest either per se or enforced by a stay in a hospital or in bed at home as the result of some illness or surgical operation sometimes materially lowers

a high blood pressure even temporarily to normal if it is not too high to start with but rarely is this effect maintained after the patient has become active again in contrast to the more lasting effect of lumbodorsal splanchnic resection when it is successful as will be recounted below (Rojas et al 1944)

Summarizing the value of the various methods of medical treatment it may be said that a few have been shown to be more useful than others, not as cures but in a palliative way. These are (1) a relief from all avoidable nervous and physical strain sometimes in the form of 'rest cures' but not an interdiction of moderate healthy outdoor exercise (2) a general reduction of diet not to a weakening starvation level but to one that prevents gain of weight or causes a moderate gradual loss of weight if there is obesity as there so often is in hypertensive cases and especially a reduction of sodium intake as in the rice diet (see above) (3) symptomatic or specific treatment of any particular complicating diseases or disorders including the eradication of such foci of infection as apical tooth abscesses (4) the trial of nerve sedatives and (5) the use of the more successful drugs namely potassium thiocyanate and especially the Veratrum derivatives under careful control as already described. Sometimes none of these measures has any effect whatsoever. Slight oscillations of blood pressure must not be regarded as important indications of the effect of treatment. Relief from all avoidable nervous and physical strain with a healthy regulation of rest, exercise, diet and bowel action is of prime importance and sometimes not possible at home where business, social and family cares are hard to escape. A holiday in some pleasant place or a visit to a good health resort at home or abroad may do much good under such circumstances. But whether carried out at home or at a health resort a fall in blood pressure though rarely to normal levels not infrequently follows such therapy.

**Surgery.** In late years there have been introduced for the treatment of hypertension certain surgical procedures. Decortication of the kidneys has proved ineffective. Excision of a deformed or diseased kidney (especially the site of cystic or pyelonephritic degeneration) with the other kidney fairly normal has cured the hypertension in a few cases justifying though to a small degree only the hopes from such a procedure based on the effect of the vascular clamp in experimental animals. Plans have been made for conservatism in such surgery so that useful renal tissue may not be sacrificed in vain. Extensive bilateral thoracic and lumbar rhizotomy though reported to be effective is too serious and dangerous an operation. The value of adrenal denervation and of subtotal adrenalectomy is now being investigated. A few spectacular cures have resulted from the exploratory discovery and removal of adrenal tumors (especially the pheochromocytoma responsible for severe paroxysmal hypertension).

**Sympathectomy** including *splanchnic nerve resection (bilateral)* introduced with the idea of causing a drop in blood pressure as the result of splanchnic and lower limb arteriolar dilatation has been developed to a high degree by a number of surgeons (Peet and associates 1935 1940 1948 Adson and Allen 1940 Smithwick 1940 1948 de Takats and associates 1942

1948 Crutchfield 1947 Poppen 1947 Grimson and Orgain 1948) some of whom most notably Smithwick now denervate both above and below the diaphragm with the result that more and more patients have secured and maintained a distinct hypotensive effect (so great in some cases that at first syncope or near syncope may occur in the erect posture) Smithwick (1940 1942) stated that removal of virtually the entire great splanchnic nerve with division of all of its aortic branches coupled with interruption of the communicating rami of D9 D10 D11 D12 and L1 together with excision of the sympathetic trunk over this area is the minimal procedure found consistently to produce a blood pressure change which is characteristic of a thorough interruption of the nerve supply to the splanchnic bed The younger patients with more labile vasopressor reactions smaller pulse pressures with relatively higher diastolic than systolic levels and less permanent cardiovascular damage have been found most amenable to improvement even though their pressures may be elevated and their fundi seriously affected (and as such belonging to the malignant hypertensive category) Spectacular improvement (perhaps cure) has been noted now in a good many cases but the procedure is still relatively new and has but recently emerged from the experimental stage

Among 224 cases sympathectomized at the Mayo Clinic (Allen and Adson 1940) good results were reported in 13 per cent fair in 18 per cent temporary in 39 per cent and poor in 30 per cent With improved technic consisting for the most part of more extensive sympathectomy better results have been obtained since 1940 Among the larger series of cases treated by experienced surgeons and with better selection than originally the results have been well worthwhile in slightly over half the patients operated upon and followed for several years For example in Smithwick's series of 256 patients with essential including malignant hypertension operated upon by his newer technic between 1938 and 1943 and followed for five to nine years the total mortality was 31.2 per cent distinctly less than the expected rate for similar hypertensive cases not so treated 90 per cent of the survivors were improved symptomatically the eye grounds were improved in 41 per cent the electrocardiograms were better in 42 per cent and the blood pressures were lower in 47 per cent (Smithwick 1948) During the first five year follow up study 84 per cent of the cases had shown a distinct lowering of pressure but a considerable number of these showed a gradual return of blood pressure toward or to the preoperative levels during the later (5 to 9 years) follow up period Palmer (1947) reported a diminishing return of favorable results the longer the patients are followed nearly 70 per cent early in his experience declining to 25 per cent when patients are followed three to five years or more But he writes this effect has been obtained twice as frequently in this series by surgical means as by a careful medical regimen and was obtained in patients with malignant hypertension whose blood pressures were unaffected by medical management Isberg and Peet (1948) have reported that 60 per cent of 384 cases of arterial hypertension were alive 5 to 12 years after splanchnicectomy of the survivors 41 per cent of those with abnormal electrocardiograms showed improvement and 44 per cent of those with preoperative

cardiac enlargement showed significant decrease in heart size. Another series of 100 consecutive patients were treated by extensive thoracolumbar sympathectomy by the same surgeon and carefully followed for 1½ to 4 years after operation the results were good in 47 per cent fair in 24 per cent and unsatisfactory in 28 per cent, including one operative death and six others who died after discharge from the hospital (Poppen and Lemmon 1947). Grimson and his associates (1949) have reported the results of subtotal to total sympathectomy in 113 patients with severe or moderately severe hypertension followed for one to nine years, 97 of the cases were still living with normal or near normal blood pressure in 31 reduced pressure in 43 more and postural lowering of pressure in all together with improvement in eye grounds in many cases and in electrocardiograms and heart size in a few.

I myself have seen many excellent results among the cases sympathectomized by Smithwick not only have the eye grounds cleared and the pressure fallen to normal or near normal but evidences of heavy strain on the heart have also abated including electrocardiographic abnormalities (Figure 97 page 477) (Canabal Thomson and White 1944 White et al 1945) and even on occasion x ray evidence of cardiac enlargement (White 1946 and Figure 98). My own most interesting experience in the treatment of serious hypertensive cardiovascular disease has been summarized in a personal study of 100 cases with important complications including for the most part left ventricular weakness or frank failure but also cerebral vascular lesions angina pectoris and past myocardial infarction. Fifty of these cases had thoracolumbar sympathectomy by Smithwick the other cases (controls) of similar sex and age distribution (ratio of 3 men to 1 woman and large majority of cases under the age of 50 in each group) and with similar defects had medical but not specific dietary treatment. Each group was followed for a minimum of three years. The mortality in a given period of time of the surgical group was less than half that of the medical group and the blood pressures eye grounds electrocardiograms and symptoms were normal or much nearer normal in the majority of the survivors of the surgical group than in the controls. The surgical cases who were not helped at all or who were worse or died were further analyzed one patient who had been improved died later of leukemia while 12 of the other 29 cases who died or were not improved could in retrospect have been quickly rejected for sympathectomy by the application of new criteria recently introduced by Smithwick (1950) in which a scoring of adverse points for various abnormalities is made and then the points added up (scores under 4 more suitable for operation than those above). For example an abnormal electrocardiogram is one adverse point x ray evidence of cardiac enlargement another age of 50 years a third and so on. Abnormality of renal function is especially serious and in general a contraindication to surgery moderate involvement of the heart however or a cerebral vascular lesion is not a bar per se. The borderline group (Smithwick's Group 3) contained 19 of my 50 sympathectomized cases 10 of which turned out well and 9 poorly it is now this group that especially needs further evaluation.

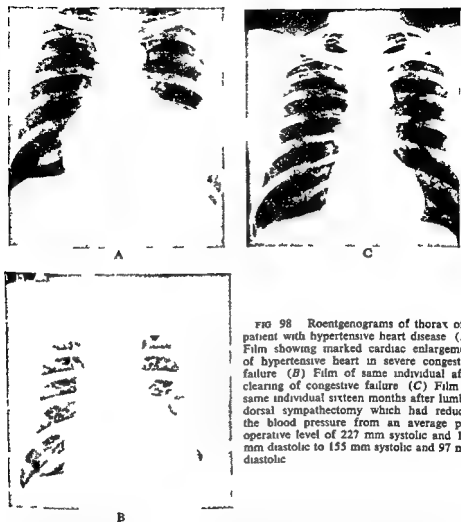


FIG 98 Roentgenograms of thorax of a patient with hypertensive heart disease (A) Film showing marked cardiac enlargement of hypertensive heart in severe congestive failure (B) Film of same individual after clearing of congestive failure (C) Film of same individual sixteen months after lumbo-dorsal sympathectomy which had reduced the blood pressure from an average pre operative level of 227 mm systolic and 120 mm diastolic to 155 mm systolic and 97 mm diastolic

The fact that 5 of my 50 hypertensive cases with grave cardiovascular lesions were perfectly well with normal blood pressure three years or more after operation and that 15 more were distinctly improved is quite clear proof in my experience that hypertensive cardiovascular disease is reversible and that up to the present time sympathectomy has achieved the greatest therapeutic success in this respect

It must be clearly recognized however that this surgical treatment is largely empirical and may be replaced or reinforced later by something better that it is a serious major operative procedure in itself (in fact two operations first on one side and then on the other ten days to two weeks apart) that it is followed by a tedious often uncomfortable convalescence lasting two or three months and that it is not suitable for the majority of patients with hyperten



sion Many cases are too old (an age under 50 years is desirable), some patients are too sick (especially if they have important kidney disease or renal insufficiency) some cases are too mild (with mostly a nervous or transient hypertension which should be watched) and many cases have mostly an arteriosclerotic hypertension with high systolic pressure (over 200 mm) and relatively low diastolic pressure (about 100 mm) allowing long survival and not requiring or appreciably helped by sympathectomy But for particular cases especially young and middle aged men with malignant hypertension and good renal function sympathectomy can be lifesaving Such indication applies of course to well under 10 per cent of all hypertensive patients

Thus as I stated seven years ago in the third edition of this book Smithwick's work represents a notable advance in the control of hypertension though we may hope that some simpler therapy or preventive measure will eventually replace operative treatment

Finally it must be said that a survey of many cases showing the serious late effects of chronic hypertension makes it evident that early discovery of hypertension at its origin by annual examinations affords the only promise for control of the disease by the earliest application of the measures outlined above until someone discovers a specific, perhaps antitoxic, cure Such a cure is being sought in the work of Page and his colleagues (1940-1949) Ferris et al. (1948) Goldblatt (1948) Schroeder (1948) Krayer and Melman (1949) Wilkins (1949), Smithwick (1949), Chasis Goldring and Smith (1949) and many others The work is, however very arduous and difficult and much patience must be exercised in awaiting the final results

(3) The care of a patient with hypertensive heart disease aside from the treatment of cardiac complications and hypertension already mentioned is like that of any chronic cardiac patient a reasonable restriction of activity and nervous strain common sense as to diet exercise and rest occasional or frequent leisurely holidays regulation of bowels, avoidance of excessive use of alcohol tobacco coffee and tea and the eradication of focal infection It is however of the greatest importance to recognize the possibility of the reversibility of even serious hypertensive heart disease by therapy at present best exemplified in the surgical procedure of sympathectomy

Finally it is of prime importance to practice preventive medicine in hypertensive families by instructing both young and old concerning the establishment of sensible health habits

**Differential diagnosis** Hypertensive heart disease is generally easy to recognize because of the presence of hypertension and of cardiac enlargement without valvular disease The onset of dilatation of heart and aorta sufficient to cause mitral and aortic systolic murmurs the occurrence of atrial fibrillation the masking of the original condition by the presence of marked congestive heart failure and especially the fall of blood pressure to normal levels may make it very difficult or even impossible to distinguish some cases of hypertensive heart disease from chronic coronary heart disease in which the history is atypical or obscure and from cardiac enlargement and failure due to

thyrotoxicosis or even to chronic rheumatic or syphilitic valvular disease. A careful history to rule out rheumatic and syphilitic infections, knowledge of physical examinations in the past which have not shown evidence of valvular disease or thyrotoxicosis, and especially careful inquiry as to a previous discovery of hypertension are often more essential in this differential diagnosis than are physical examination and laboratory tests carried out at the moment when the decision must be made.

## HYPOTENSION

Hypotension that is a systolic blood pressure below 100 mm of mercury does not cause heart disease although it sometimes accompanies it as in the case of aortic stenosis or acute heart failure from cardiac infarction (due to coronary thrombosis). Low blood pressure is more commonly found in the absence of heart disease than in its presence, especially in certain weak and frail individuals in chronic wasting disease, temporarily in peripheral vascular failure or shock (see Chapter 31) or in attacks of neurocirculatory asthenia or of paroxysmal tachycardia with excessively rapid heart rates. In a few cases of marked carotid sinus reflex, in the rare cases of adrenal (Addison's) disease, and in a few individuals as a postural phenomenon where it has been called orthostatic or essential hypotension.

Postural hypotension has been called a disease of the sympathetic nervous system by Stead and Ebert (1941) whether peripheral or central is not clear though the latter is favored (Hermann 1947). Patients with this condition do not apparently pool more blood in the lower part of the body on standing than do normal subjects but they lack the reflex vasoconstriction which maintains the arterial pressure in normal subjects when erect; this phenomenon may appear acutely and temporarily in healthy persons after very strenuous exercise (Eichna et al 1947) and it is of course quite common for a few weeks after thoracolumbar sympathectomy for hypertension.

An abdominal support, elastic stockings, paddedine (Yukis and Griffith 1948) and angiotonin and the head up bed (Corcoran et al 1942) have given relief.

## BIBLIOGRAPHY

### HYPERTENSION AND HYPERTENSIVE HEART DISEASE HYPOTENSION

#### Hypertension and Hypertensive Heart Disease Etiology, Diagnosis and Course

- Alam G M and Smirk F H. Casual and Basal Blood Pressure. I. In British and Egyptian Men. II. In Essential Hypertension. *Brit Heart J* 1943 V 152.
- Ayman D and Goldshine A D. Blood Pressure Determinations by Patients with Essential Hypertension. II. Difference Between Home and Clinic Readings During and After Treatment. *Am J M Sc* 1941 CCI 157.
- Bell E T and Clawson H J. Primary (Essential) Hypertension. *Arch Path* 1928 V 939.
- Blackford J M and Wilkinson J N. "Hypertension—A Study of Two Hundred Two Cases Followed for an Average Period of Ten Years with Remarks on Causes and Treatment." *Ann Int Med* 1932 VI 54.

- Bright R Cases and Observations Illustrative of Renal Disease *Guys Hosp Rep* 1836 I 338
- Castleman B and Smithwick R H "The Relation of Vascular Disease to the Hypertensive State Based on a Study of Renal Biopsies from One Hundred Hypertensive Patients" *JAMA* 1943 CXXI 1256
- Clawson II J Incidence of Types of Heart Disease Among 30 265 Autopsies with Special Reference to Age and Sex *Am Heart J* 1941 XXII 607
- Corcoran A C and Page I J Arterial Hypertension Correlation of Clinical and Experimental Observations" *JAMA* 1941 CXVI 690
- Cushing H The Basophil Adenomas of the Pituitary Body and Their Clinical Manifestations *Bull Johns Hopkins Hosp* 1932 L 137
- Davis II and Klainer M J Studies in Hypertensive Heart Disease *Am Heart J* 1940 XIX 185 198 and XX 98
- Davison C and Brill N Q Essential Hypertension and Chronic Hypertensive Encephalopathy *Ann Int Med* 1939 XII 1766
- Fahr G E Hypertension Heart The Most Common Form of So Called Chronic Myocarditis *JAMA* 1923 LXXX 981 and 1935 CV 1396
- Fahr Th "Über die Beziehungen von Arteriosklerose Hypertonie und Herzhypertrophie" *Virch Arch f path Anat* 1922 CCXXXIX 41
- Garvin C F Functional Aortic Insufficiency *Ann Int Med* 1940 XIII 1799
- Gilchrist A R A Honyman Gillespie Lecture on the Hypertensions *Edinburgh M J* 1941 XLVIII 752
- Goldblatt H et al Studies on Experimental Hypertension I The Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia *J Exper Med* 1934 LIX 347 *Arch Surg* 1941 XLIII 327
- Gull W W and Sutton H G On the Pathology of the Morbid State Commonly Called Chronic Bright's Disease with Contracted Kidney (Arterio-Capillary Fibrosis) *M Chir Tr London* 1872 LV 273
- Harrison T R Grollman A and Williams J R Jr Antipressor Action of Renal Extracts and Their Capacity to Reduce Blood Pressure of Hypertensive Rats" *Am J Physiol* 1940 CXXVIII 716
- Hines E A Jr The Hereditary Factor in Essential Hypertension *Ann Int Med* 1937 XI 593
- Hines E A Jr and Brown G II The Cold Pressor Test for Measuring the Reactivity of the Blood Pressure Data Concerning 571 Normal and Hypertensive Subjects *Am Heart J* 1936 XI 1
- Houssay II A Fasciolo J C and Taquini A C Mecanismo de la hipertension arterial de origen renal *Rev Argentina d Cardiol* 1938 V 291
- Keith N M Wagener H P and Kernohan J W The Syndrome of Malignant Hypertension *Arch Int Med* 1928 XLI 141
- Levine V Myocardial Changes in Hypertension" *Arch Path* 1934 XVIII 331
- Murphy F D Grill J Pessin II and Moxon G "Essential (Primary) Hypertension A Clinical and Morphological Study of 375 Cases" *Ann Int Med* 1932 VI 31
- Oppenheimer B S and Fishberg A M "Hypertensive Encephalopathy" *Arch Int Med* 1978 XLI 264
- Page I H and Helmer O M A Crystalline Pressor Substance (Angiotonin) Resulting from the Reaction Between Renin and Renin activator" *J Exper Med* 1940 LXXI 29
- Paullin J E Bowcock H M and Wood R H "Complications of Hypertension" *Am Heart J* 1927 II 613
- Pickering G W "The Problem of High Blood Pressure in Man" *Brit M J* 1939 I 1 and *J Mt Sinai Hosp* 1942 VIII 916
- Selye H Hall C E and Rowley E M "Malignant Hypertension Produced by Treatment with Desoxycorticosterone Acetate and Sodium Chloride" *Canad M A J* 1943 XLIX III
- Steele J M and Cohn A E "The Nature of Hypertension in Coarctation of the Aorta" *J Clin Investigation* 1938 XVII 514
- Stewart, C F "Arteriosclerosis of the Renal Artery Orifices with Severe Hypertension." *JAMA* 1940 CXIV 2099

- Taussig, H B and Remsen D B "Essential Hypertension in Boy of Two Years of Age" *Bull Johns Hopkins Hosp* 1935 LVII 183
- Tigerstedt R. and Bergmann, P G Niere und Kreislauf" *Skand Arch Physiol* 1898 VIII 223
- Weiss S and Parker F Jr "Pyelonephritis Its Relation to Vascular Lesions and to Arterial Hypertension" *Medicine* 1939 XVIII 221
- White P D A Note on the Common Occurrence of Serious Involvement of the Heart in Hyperpiesia" *New England J Med* 1936 CCXIV 719
- White P D and Jones T D Heart Disease and Disorders in New England" *Am Heart J* 1928 III 302
- Wood J E Jr and Cash J R "Experimental Hypertension Observations on Sustained Elevation of Systolic and Diastolic Blood Pressure in Dog" *J Clin Investigation* 1936 XV 543

#### Recent References (1944-1950)

- Armstrong H G and Rafferty J A "Cold Pressor Test Follow up Study for Seven Years on 166 Officers" *Am Heart J* 1950 XXXIX 484
- Bechgaard P "Electrocardiogrammet hos 264 ubehandlede hypertonikere En efterundersøgelse" *Nord med* 1949 XLII 1803 and "Electrocardiographic Investigation of 264 Cases of Hypertension" *Brit M J* 1949 II 1089
- Bridges W C Johnson A L Smithwick R H and White P D Electrocardiography in Hypertension Study of Patients Subjected to Lumbodorsal Splanchnicectomy" *JAMA* 1946 CXXXI 1476
- Burgess A M Excessive Hypertension of Long Duration" *New England J Med* 1948 CCXXXIX 75
- Canabal E J Warneford Thomson H F and White P D "The Electrocardiogram in Hypertension III Electrocardiograms of Hypertensive Patients Followed for a Long Time Without Splanchnic Resection in Comparison With Those in Patients Who Had Had Splanchnic Resection" *Am Heart J* 1945 XXX 189
- Castleman H and Smithwick R H "The Relation of Vascular Disease to the Hypertensive State II The Adequacy of the Renal Biopsy as Determined from a Study of 500 Patients" *New England J Med* 1948 CCXXXIX 729
- Currens J H A Comparison of the Blood Pressure in the Lying and Standing Positions A Study of Five Hundred Men and Five Hundred Women" *Am Heart J* 1948 XXXV 646
- Evans E Mathews M and White P D "The Electrocardiogram in Hypertension I Its Description" *Am Heart J* 1945 XXX 140
- Evelyn, K. A "A Long Term Study of the Natural History of Essential Hypertension" *Ann Int Med* 1950 XXXIII 629
- Ferris E B Reiser M F Stead W W and Brust A A Jr "Clinical and Physiological Observations of Interrelated Mechanisms in Arterial Hypertension" *Tr A Am Physicians* 1948 LXI 97
- Frant R and Groen J "Prognosis of Vascular Hypertension Nine Year Follow up Study of 418 Cases" *Arch Int Med* 1950 LXXXV 727
- Goldblatt H *The Renal Origin of Hypertension* Charles C Thomas Publisher Springfield Ill 1948
- Goodman L "Recurrent Hypertensive Cerebral Thrombosis Clinicopathologic Analysis of 6 Cases with Discussion of Pathogenesis" *Arch Neurol & Psychiat* 1950 LXII 445
- Gressel G C Shobe F O Saslow G DuBois P H and Schroeder H A "Personality Factors in Arterial Hypertension," *JAMA* 1949 CXL 265
- Griep A H Barry G R Hall W C and Hoobler S W "The Prognosis in Arterial Hypertension Report on 117 Patients Under 53 Years of Age Followed 8 to 10 Years" *Am J M Sc* 1951 CCXXI 239
- Hammarstrom S "Arterial Hypertension I Variability of Blood Pressure Neurological Treatment Indications and Results" *Acta med Scandinav* 1947 Suppl 197 1
- Hayes F W Dexter L and Seibel R E "Renin Content of Renal Venous Blood of Normal and Hypertensive Patients at Rest" *Am J Physiol* 1947 CL 198

- Hillman C C Levy R L Stroud W D and White P D Studies of Blood Pressure in Army Officers Observations Based on an Analysis of the Medical Records of 27741 Officers of the U S Army *JAMA* 1944 CXXV 699
- Levy R L Hillman C C Stroud W D and White P D Transient Hypertension Its Significance in Terms of Later Development of Sustained Hypertension and Cardiovascular Renal Diseases *JAMA* 1945 CXXVI 829
- Lichtwitz A Le Bihan A Delaville M and Thomopoulos H Proteines et hypertension artérielle Les hypertensions carentielles *La Semaine des Hop* 1950 XXVI 371
- Lups B and Francke C Changes in Blood Pressure During Period of Starvation (January 1944 to May 1945) and After Liberation (May 1945 to September 1945) in Utrecht Holland *Acta med Scandinavica* 1947 CXXVI 449
- Murphy B W Emotional Aspects of Essential Hypertension *New Zealand M J* 1950 XLIX 284
- Ordman B A Review of the Incidence of Hypertension in the Non European Races Survey of Blood Pressure in the South African Bantu *Clin Proc Cape Town* 1948 VII 183
- Page I H Pathogenesis of Arterial Hypertension *JAMA* 1949 CXL 451
- Page I H and Corcoran A C *Arterial Hypertension* The Year Book Publishers Inc Chicago 2nd ed 1949 (1st ed 1945)
- Palmer R S Psyche and Blood Pressure One Hundred Mental Stress Tests and Fifty Personality Surveys in Patients with Essential Hypertension *JAMA* 1950 CXLIV 295
- Palmer R S Loofbourow D and Doering C R Prognosis in Essential Hypertension *New England J Med* 1948 CCXXXIX 990
- Palmer R S Nyssens A F and White J C Severe Hypertension with Papilledema Simulating Brain Tumor *New England J Med* 1948 CCXXXIX 322
- Pickering G W Transient Cerebral Paralysis in Hypertension and in Cerebral Embolism With Special Reference to the Pathogenesis of Chronic Hypertensive Encephalopathy *JAMA* 1948 CXXVII 423
- Raab W Hypertension and Tachycardia Due to Concussion of the Brain *Am Heart J* 1949 XXXVII 237
- Schroeder H A and Goldman M L Pressor Substances in Extracts of Hypertensive Blood *J Clin Investigation* 1948 XXVII 555
- Schroeder H A and Olsen N S "Pressor Substances in Arterial Hypertension II Demonstration of Pherentasin a Vasoactive Material Procured from Blood" *J Exper Med* 1950 XCII 445
- Selye H The General Adaptation Syndrome and the Diseases of Adaptation *J Clin Endocrinol* 1946 VI 117
- Suárez R M Incidence of Hypertension in Puerto Rico *Ann Int Med* 1950 XXXIII 346
- Taquini A C and Fasciolo J C Renin in Essential Hypertension *Am Heart J* 1946 XXXII 357
- Taylor R D Corcoran A C and Page I H Menopausal Hypertension Critical Study *Am J M Sc* 1947 CCXIII 475
- "A Hormonal Neurogenic Vasopressor Mechanism" *Arch Int Med* 1951 LXXXVIII 1
- Vakil M J A Study of Hypertensive Heart Disease in India (538 Cases of Hypertensive Heart Disease in a Total Medical In Patient Population of 30104 Patients at the King Edward Memorial Hospital Bombay) *Indian Heart J* 1950 II 31
- White P D The Heart in Hypertension Since the Days of Richard Bright *Canad M A J* 1946 LIV 129
- White P D Smithwick E H Mathews M W and Evans E The Electrocardiogram in Hypertension II The Effect of Radical Lumbodorsal Sympathectomy *Am Heart J* 1945 XXX 165
- Wolf S Pfeiffer J B Ripley H S Winter O S and Wolff H C Hypertension as a Reaction Pattern to Stress Summary of Experimental Data on Variations in Blood Pressure and Renal Blood Flow *Ann Int Med* 1948 XXIX 1056

## Pheochromocytoma

- Bartels E C and Cattell R B "Pheochromocytoma Its Diagnosis and Treatment" *Ann Surg* 1950 CXXXI 903
- Goldenberg M and Aranow H Jr "Diagnosis of Pheochromocytoma by the Adrenergic Blocking Action of Benzodioxan" *JAMA* 1950 CXLIII 1139
- Goldenberg M Snyder C H and Aranow H Jr "New Test for Hypertension Due to Circulating Epinephrine" *JAMA* 1947 CXXXV 971
- Green H M "Pheochromocytoma and Chronic Hypertension" *JAMA* 1946 CXXXI 1260
- Howard J F and Barker W H "Paroxysmal Hypertension and Other Clinical Manifestations Associated with Benign Chromaffin Cell Tumors (Pheochromocytomata)" *Bull Johns Hopkins Hosp* 1937 LXI 371
- Labbe M et al "Crises solaires et hypertension paroxystique en rapport avec une tumeur surrenal" *Bull et mem d l soc med d hop d Paris* 1922 XLVI 982
- Pitcairn D M and Youmans W B "The Nature of Pressor Substances in Pheochromocytomas" *Circulation* 1950 II 505
- Roth G M and Kvale W F "A Tentative Test for Pheochromocytoma" *Am J M Sc* 1945 CCX 653
- "Pharmacologic Tests as an Aid in Diagnosis of Pheochromocytoma" *Mod Concepts Cardiovas Dis* 1949 XVIII No 5
- Smithwick R H Greer W E R Robertson C W and Wilkins R W "Pheochromocytoma A Discussion of Symptoms Signs and Procedures of Diagnostic Value" *New England J Med* 1950 CCXLII 252
- Snyder C H and Vick E H "Hypertension in Children Caused by Pheochromocytoma Report of 3 Cases and Review of the Literature" *Am J Dis Child* 1947 LXXIII 581
- Van Epp E W Hyndman O R and Green J A "Clinical Manifestations of Paroxysmal Hypertension Associated with Pheochromocytoma of Adrenal" *Arch Int Med* 1940 LV 1123
- Wells A H and Boman P G "The Clinical and Pathologic Identity of Pheochromocytoma" *JAMA* 1937 CIX, 1176

## Treatment Drugs

- Barker M H Lindberg H A and Wald M H "Experiences with Thiocyanates" *JAMA* 1941 CXVII 1591
- Blaney L F Geiger A J and Ernst H G "Potassium Thiocyanate in Treatment of Hypertension" *Yale J Biol & Med* 1941 XIII 493
- Caviness V S and associates "Potassium Sulfocyanate in Treatment of Hypertension" *North Carolina M J* 1941 II 283 and *Am J M Sc* 1942 CCIV 688
- Evans W and Loughnan O "The Drug Treatment of Hyperpiesta" *Brit Heart J* 1939 I 199
- Fanson E Kinsey D and Palmer R S "Potassium Sulfocyanate Therapy in Essential Hypertension" *New England J Med* 1943 CCXXIX 540
- Grollman A Williams J R and Harrison T R "Reduction of Elevated Blood Pressure by Administration of Renal Extracts" *JAMA* 1940 CXV 1169
- Page I H and associates "The Reduction of Arterial Blood Pressure of Hypertensive Patients and Animals with Extract of Kidney" *J Exper Med* 1941 LXXIII 7 and *Arch Int Med* 1941 XV 347
- Robinson R W and O'Hare J F "Further Experiences with Potassium Sulfocyanate Therapy in Hypertension" *New England J Med* 1939 CCXXI 964
- Wald M H Lindberg H A and Barker M H "The Toxic Manifestations of the Thiocyanates" *JAMA* 1939 CXII 1140

## Recent References (1944-1950)

- Alstad K S "The Effects of Thiocyanate on Basal and Supplemental Blood Pressures" *Brit Heart J* 1949 XI 249
- Beckmann F "Über die Möglichkeiten der intravenösen Verwendung von Novocain

- und der Hochdruckbehandlung mit Melcam *Deutsch med Wchnschr* 1950 LXXV 426
- Bello C T Moss W G and Weiss E Effects of Orally Administered Dihydroergocornine (DHO 180) on Hypertension *Am J Med* 1950 VIII 634
- Coe W S Best M M and Kinsman J M "Veratrum Viride in the Treatment of Hypertensive Vascular Disease" *JAMA* 1950 CXLIII 5
- Connor R G Emlet J R and Grimson K S Effects of Veriloid Intravenously in Dogs and Intravenously and Orally in Patients *J Pharmacol & Exper Therap* 1951 CI 8
- Donegan C K Messer A L Orgain E S and Ruffin J M "Negative Results in Tocopherol Therapy in Cardiovascular Disease" *Am J M Sc* 1949 CCXVII 294
- Fischmann E J and Fischman A Thiocyanate in Hypertension Blood Pressure Behavior after Withdrawal of the Drug and Serial Electrocardiograms as Criteria of Response" *Am Heart J* 1950 XXXIX 477
- Freis E D Veratrum Viride and Hypertension *JAMA* 1950 CXLIV 1023
- Freis E D and Stanton J R A Clinical Evaluation of Veratrum Viride in the Treatment of Essential Hypertension" *Am Heart J* 1948 XXXVI 723
- Freis E D Stanton J R and Wilkins R W The Effects of Certain Dihydrogenated Alkaloids of Ergot in Hypertensive Patients *Am J M Sc* 1948 CCXVI 163
- Griffith J Q Jr and Lindauer M A "Rutin Therapy for Capillary Abnormality in Hypertension" *Ohio State M J* 1947 XLIII 1136
- Grimson K S Reardon M J Marzoni F A and Hendrix J P The Effects of Priscol (2 benzyl-4 5 imidazoline HCl) on Peripheral Vascular Diseases Hypertension and Circulation in Patients *Ann Surg* 1948 CCXXVII 968
- Hoobler S W et al Effects of Protoveratrine on the Circulation in Hypertension *J Clin Investigation* 1951 XXX 631
- Jal Vakil R A Clinical Trial of Rauwolfia Serpentina in Essential Hypertension *Brit Heart J* 1949 XI 350
- Krayer O "Progress in the Chemistry and Pharmacology of the Veratrum Alkaloid Program" *Am Soc Pharmacol & Exper Therap* Nov 13 1950 p 5
- Locket S et al Methonium Compounds in Treatment of Hypertension" *Brit Med J* 1951 I 778
- Lyons R H Hoobler S W Neligh R B Moe G K and Peet M M "Experiences with Tetraethylammonium Chloride in Hypertension" *JAMA* 1948 CXXXVI 608
- Meilman E and Krayer O Clinical Studies on the Pure Veratrum Alkaloids Protoveratrine and Veratridine *J Clin Investigation* 1949 XXVIII 798
- "The Effects of Protoveratrine A Pure Veratrum Alkaloid in Hypertensive Patients *J Clin Investigation* 1950 XXIX 833
- Menof, P "Essential Hypertension Its Control by New Method Preliminary Report *South African M J* 1950 XXIV 172
- Ruskin A and McKinley W F Comparative Study of Potassium Thiocyanate and Other Drugs in the Treatment of Essential Hypertension" *Am Heart J* 1947 XXIV 691
- Smirk F H Methonium Halides in High Blood Pressure" *Science* 1951 CXIV 4
- Stutzman J W and Maillon G L "Hypotensive Action of Veriloid An Extract of Veratrum Viride *Fed Proc Fed of Am Soc for Exper Biol* 1950 IX 318
- Tandowsky R M "The Clinical Effect of Dihydroergocornine Methanesulphonate (DHO 180) in Arterial Hypertension A Preliminary Report" *Circulation* 1950 I 686
- Wilkins R W Stanton J R and Freis E D "Essential Hypertension Therapeutic Trial of Veriloid New Extract of Veratrum Viride *Proc Soc Exper Biol & Med* 1949 LXXII 302
- Wunsch R E Warne R B and Myers G B "The Effects of Dibenamine on Severe Hypertension" *Ann Int Med* 1950 XXXIII 613

#### Treatment. Diet

- Allen, F M "Arterial Hypertension" *JAMA* 1920 LXXIV 652
- Bang, H B Bechgaard P and Nielsen, A L "Low Salt Diet in Treatment of Hypertension and Hypertensive Heart Disease" *Brit M J* 1949 II 1203

- Cameron B R, Dunlop D N, Platt R, Rosenheim, M L, and Sharpey Schafer E P "The Rice Diet in the Treatment of Hypertension. A Report to the Medical Research Council" *Lancet* 1950 II, 509
- Chapman, C B., and Gibbons T II "The Diet and Hypertension" *Medicine* 1950 XXIX, 29
- Chapman, C B, Gibbons T and Henschel A "The Effect of the Rice Fruit Diet on the Composition of the Body" *New England J Med* 1950 CCXLIII 899
- Chasis H, Goldring, W, Breed E, Bolomey A, and Smith, H W "Effects of Salt and Protein Restriction on Blood Pressure and Renal Hemodynamics in Hypertensive Patients" *J Clin Investigation* 1949 XXVIII 775
- Corcoran, A C, Taylor R D, and Page I H "Controlled Observations on the Effect of Low Sodium Dietotherapy in Essential Hypertension" *Circulation* 1951 III 1
- Currens J II, Reid E A S, MacLachlan E A, Terry M L, Butler A. M, and White P D "Physiologic Metabolic and Electrolytic Balance Studies of Hypertensive Patients While on the Rice Diet." *J Clin Investigation* 1949 XXVIII 776
- Flipse M E., and Flipse M J "Observations in Treatment of Hypertension with Rice Fruit Diet." *South M J* 1947 XL 721
- Kempner W "Treatment of Kidney Disease and Hypertensive Vascular Disease with Rice Diet" *North Carolina M J* 1944 V 125 and 273 1945 VI 61 117
- "Treatment of Hypertensive Vascular Disease with Rice Diet." *Am J Med* 1948 IV 545
- "Treatment of Heart and Kidney Disease and of Hypertensive and Arteriosclerotic Vascular Disease with the Rice Diet" *Ann Int Med* 1949 XXXI 821
- Kert, M J et al "Treatment of Hypertension Experiences with the Use of a Low Sodium Diet other than the Rice Diet A Preliminary Report." *JAMA* 1950 CXLIII, 721
- Landowne M, Thompson, W S Jr and Ruby B "The Manual Sodium Diet A Controlled Study of Its Effect Upon the Blood Pressure of Ambulatory Hypertensive Patients." *J Lab & Clin Med* 1949 XXXIV 1380
- Loofbourow D G, Callahan, D, and Palmer R. S "The Rice Diet in Ambulatory Patients with Essential Hypertension. A Two-Year Study of 105 Patients" *New England J Med* 1951 CCXLIV 577
- Loofbourow D G, Galbraith A L, and Palmer R. S "Effect of Rice Diet on Level of Blood Pressure in Essential Hypertension" *New England J Med* 1949 CCXL, 910
- Schwartz, W B, and Merlis J K "Nitrogen Balance Studies on the Kempner Rice Diet." *J Clin Investigation* 1948 XXVII 555
- Stead W W, Reiser M F, Rapoport, S, and Ferris E II "The Effect of Sodium Chloride Depletion on Blood Pressure and Tetraethylammonium Chloride Response in Hypertension" *J Clin Investigation* 1948 XXVII 766
- Ucko H "Dietary Treatment of Hypertension" *Brit M J* 1950 II 144
- Watkins II M "Nitrogen and Electrolyte Balance in Hypertensive Patients on the Rice Diet" *J Clin Investigation* 1950 XXIX, 851
- Watkins II M, Froeb H F, Hatch, F T, and Gutman A B "Effects of Diet in Essential Hypertension I Baseline Study Effects in 86 Cases of Prolonged Hospitalization on Regular Hospital Diet"
- "II Results with Unmodified Kempner Rice Diet in 50 Hospitalized Patients" *Am J Med* 1950 IX, 428 and 441
- Weston R. E, Hellman, L, Escher D J W, and Lester L. "Effect of Low Sodium and Kempner Diets on Renal Hemodynamics and Electrolyte Excretion in Hypertensives" *Federat on Proc Fed of Am Soc of Exper Biol.*, 1948 VII 132
- Williamson, C R. "Observations on the Management of Hypertension by the Kempner Rice Diet." *New England J Med* 1950 CCXLIII 177

#### Treatment. Sympathectomy

- Adson A W., and Brown G E "Malignant Hypertension. Report of Case Treated by Bilateral Section of Anterior Spinal Nerve Roots from the Sixth Thoracic to the Second Lumbar Inclusive" *JAMA.*, 1934 CII 1115
- Allen E V., and Adson A W "The Treatment of Hypertension Medical versus Surgical" *Ann Int Med* 1940 XIV 288



- und der Hochdruckbehandlung mit Melcam *Deutsch med Wchnschr* 1950 LXXV 426
- Bello C T Moss W G and Weiss E Effects of Orally Administered Dihydroergocornine (DHO 180) on Hypertension *Am J Med* 1950 VIII 634
- Coe W S Best M M and Kinsman J M Veratrum Viride in the Treatment of Hypertensive Vascular Disease *JAMA* 1950 CXLIII 5
- Connar R G Emlet J R and Grimson K S Effects of Veriloid Intravenously in Dogs and Intravenously and Orally in Patients *J Pharmacol & Exper Therap* 1951 CI 11
- Donagan C K Messer A L Orgain E S and Ruffin J M Negative Results in Tocolchol Therapy in Cardiovascular Disease *Am J M Sc* 1949 CCXVII 294
- Fischmann E J and Fischman A Thiocyanate in Hypertension Blood Pressure Behavior after Withdrawal of the Drug and Serial Electrocardiograms as Criteria of Response *Am Heart J* 1950 XXXIX 477
- Freis E D Veratrum Viride and Hypertension *JAMA* 1950 CXLIV 1073
- Freis E D and Stanton J R A Clinical Evaluation of Veratrum Viride in the Treatment of Essential Hypertension *Am Heart J* 1948 XXXVI 723
- Freis E D Stanton J R and Wilkins R W The Effects of Certain Dihydrogenated Alkaloids of Ergot in Hypertensive Patients *Am J M Sc* 1948 CCXVI 163
- Griffith J Q Jr and Lindauer M A Rutin Therapy for Capillary Abnormality in Hypertension *Ohio State M J* 1947 XLIII 1136
- Grimson K S Reardon M J Marzoni F A and Hendrix J P "The Effects of Priscol (2 benzyl-4,5 imidazole HCl) on Peripheral Vascular Diseases Hypertension and Circulation in Patients" *Ann Surg* 1948 CXXXVII 968
- Hoobler S W et al Effects of Protoveratrine on the Circulation in Hypertension *J Clin Investigation* 1951 XXX 651
- Jal Vakil R A Clinical Trial of Rauwolfia Serpentina in Essential Hypertension *Brit Heart J* 1949 XI 350
- Krayer O Progress in the Chemistry and Pharmacology of the Veratrum Alkaloid Program *Am Soc Pharmacol & Exper Therap* Nov 13 1950 p 5
- Locket S et al "Methonium Compounds in Treatment of Hypertension" *Brit Med J* 1951 I 778
- Lyons R H Hoobler S W Neligh R H Moe G K and Peet M M Experiences with Tetraethylammonium Chloride in Hypertension *JAMA* 1948 CXXXVI 608
- Meilman E and Krayer O Clinical Studies on the Pure Veratrum Alkaloids Protoveratrine and Veratridine *J Clin Investigation* 1949 XXVIII 798
- "The Effects of Protoveratrine A Pure Veratrum Alkaloid in Hypertensive Patients *J Clin Investigation* 1950 XXIX 833
- Menof P "Essential Hypertension Its Control by New Method Preliminary Report *South African M J* 1950 XXIV 172
- Ruskin A and McKinley W F "Comparative Study of Potassium Thiocyanate and Other Drugs in the Treatment of Essential Hypertension *Am Heart J* 1947 XXXIV 691
- Smirk F H "Methonium Halides in High Blood Pressure *Science* 1951 CXIV 4
- Stutzman J W and Mason G L "Hypotensive Action of Veriloid An Extract of Veratrum Viride *Fed Proc Fed of Am Socs for Exper Biol* 1950 IX 318
- Tandowsky R M "The Clinical Effect of Dihydroergocornine Methanesulphonate (DHO 180) in Arterial Hypertension A Preliminary Report" *Circulation* 1950 I 686
- Wilkins R W Stanton J E and Freis E D "Essential Hypertension Therapeutic Trial of Veriloid New Extract of Veratrum Viride" *Proc Soc Exper Biol & Med* 1949 LXXII 302
- Wunsch E E Warnke R D and Myers G B "The Effects of Dibenamine on Severe Hypertension" *Ann Int Med* 1950 XXXIII 613

#### Treatment. Diet

- Allen F M "Arterial Hypertension" *JAMA* 1920 LXXIV 652
- Bang H B Bechgaard P and Nielsen A L "Low Salt Diet in Treatment of Hypertension and Hypertensive Heart Disease" *Brit M J* 1949 II 1203

- Pect M M and Isberg E M "The Problem of Malignant Hypertension and Its Treatment by Splanchnic Resection" *Ann Int Med* 1948 XXVIII, 755
- "The Treatment of Hypertensive Cerebrovascular Disease by Splanchnicectomy" *New England J Med* 1949 CCXL 319
- Poppen J L and Lemmon C "The Surgical Treatment of Essential Hypertension" *JAMA* 1947 CXXXIV 1
- Rogers W F and Palmer R S "Essential Hypertension: Prognosis and Comparison of Medical and Surgical Treatments" *Am Pract* 1947 I, 459
- Rojas F Smithwick R H and White P D "Nonspecific Major Operations and Lumbodorsal Sympathectomy: A Comparison Between Their Effect on the Blood Pressure" *JAMA* 1944 CXXXVI 15
- Smithwick R H "Continued Hypertension: Prognosis for Surgically Treated Patients" *Brit Med J* 1948 II 237
- "The Surgical Physiology of Hypertension" *S Clin North America* 1949 XXIX 1699
- Taquini A C and Villamil A "Modificaciones del volumen sanguineo determinadas por la simpatectomia toracolumbar (Smithwick) en hipertensos" *Medicina* 1949 IX 352
- Thorpe J J Welch W J and Poindexter C A "Bilateral Thoracolumbar Sympathectomy for Hypertension: Study of 500 Cases" *Am J Med* 1940 IX 500
- White P D "The Reversibility of Hypertensive Heart Disease by Lumbodorsal Sympathectomy" *Wisconsin M J* 1946 XLV 1135
- White P D Smithwick R H Mathews M W and Evans E "The Electrocardiogram in Hypertension. II The Effect of Radical Lumbodorsal Sympathectomy (Preliminary Report)" *Am Heart J* 1945 XXX 165
- White P D Diamond E G and Williams A "Comparative Follow up Study of 50 Hypertensive Private Patients with Cardiovascular Complications (Angina Pectoris, Healed Myocardial Infarction, Left Ventricular Failure or Cerebral Vascular Accidents) Treated by Lumbodorsal Sympathectomy (Carried Out by Reginald Smithwick 1941 to 1946) and 50 Control Patients Treated Medically" *JAMA* 1950 CXLIII 1311
- Wilkin R W Culbertson J W and Halperin M H "The Hemodynamic Effects of Sympathectomy in Essential Hypertension" *Ann Int Med* 1949 XXX 291

#### Treatment Miscellaneous

- Baird P C Lingley J M and Palmer R S "The Failure of Roentgen Ray Therapy of Pituitary and Adrenals in Essential Hypertension" *New England J Med* 1934 CCXI 952
- DeNunzio R "Prime tecniche cliniche sull'azione ipotensiva d'ell-olio" *Revista di Clin Med Firenze* 1947 XLVII 511
- Gasul B M Glasser J M and Grossman A "Extreme Hypertension in a Child Cured by Nephrectomy: Report of a Case and Review of the Literature" *JAMA* 1949 CXXXIX, 305
- Jeffers W A et al "The Blood Pressure of Patients with Hypertension After Subtotal Adrenalectomy: Relationship to the Amount of Residual Adrenal Tissue and Substitution Therapy" *J Clin Investigation* 1951 XXX 652
- Page I H and Taylor R D "Pyrogens in the Treatment of Malignant Hypertension" *Mod Concepts Cardiac Dis.* 1949 XVIII No 10
- Ratliff R K Nesbit R M Plumb R T and Bohne W "Nephrectomy for Hypertension with Unilateral Renal Disease: Report of Forty nine Cases" *JAMA* 1947 CXXXIII 296

#### Hypotension

- Corcoran A C Browning J S and Page I H "Renal Hemodynamics in Orthostatic Hypotension: Effects of Angiotonin and Head Up Bed" *JAMA* 1947 CXIX 793
- Eichna L W Horvath S M and Bran W B "Post-exertional Orthostatic Hypotension" *Am J Med Sc* 1947 CCXIII 641
- Ellis L B and Hynes F W "Postural Hypotension with Particular Reference to Its Occurrence in Disease of Central Nervous System" *Arch Int Med* 1936 LVIII 773

Friedlander A Clinical Types of Hypotension *JAMA* 1924 LXXXIII 167  
 Ghrist D G and Brown G E Postural Hypotension with Syncope Its Successful Treatment with Ephedrin *Am J M Sc* 1928 CLXXV 336  
 Hermann H Lhypotension orthostatique essentielle sa physio pathologie ses enseignements physiologiques *Bruxelles Med* 1947 XXVII 1875  
 Korns H M and Randall W L Orthostatic Hypotension Treated with Benzedrine Report of Case *Am Heart J* 1937 XIII 114  
 Stead E A Jr and Ebert H V Postural Hypotension Disease of Sympathetic Nervous System *Arch Int Med* 1941, LXVII 546  
 Yuskis A H and Griffith G C Orthostatic Hypotension and Orthostatic Tachycardia New Clinical Observations Successful Treatment with Paredrine and Review of Literature *California Med* 1948 LXIX, 255

---

## CHAPTER 20

---

### PULMONARY HEART DISEASE ACUTE AND CHRONIC COR PULMONALE PULMONARY HYPERTENSION

---

**Introduction** During the past seven years since the publication of the third edition of this book there have been distinct advances both in the clinical recognition of the frequency of pulmonary embolism in medical especially cardiac cases along with better diagnostic criteria and also in the introduction of preventive measures thus reducing the incidence of the complication of the acute cor pulmonale. Also the application of improved industrial hygiene and of more specific measures to reduce pulmonary infections will doubtless result in time in a decreased incidence of the chronic cor pulmonale.

The effect of pulmonary hypertension on the right ventricle is comparable to that of systemic hypertension on the left ventricle except that in the case of the pulmonary circulation there are more instances of *sudden unexpected* great increase in blood pressure to cause acute right ventricular strain. Pulmonary hypertension originates in the great majority of cases in seven different ways in the first place and most commonly from dilatation and failure of the left ventricle abrupt or gradual secondly and fairly often from mitral valve deformity with or without stenosis thirdly and also frequently and always abruptly from massive pulmonary embolism fourthly and usually to but a slight extent from chronic pulmonary disease including fibrosis and emphysema fifthly importantly but not often from the pressure of inhaled dust in particular silica sixthly from the more marked grades of chest deformity due to high degrees of kyphoscoliosis or compression (not displacement) of the heart by the funnel chest and finally and rarely from primary disease of the pulmonary arteries and arterioles. There are also excessively rare instances of acute subacute or chronic cor pulmonale secondary to obstruction of the pulmonary circulation by metastatic malignancy or by high degrees of diaphragmatic herniation with compression of the thoracic contents by stomach and intestines.

The first factor left ventricular dilatation and failure will be discussed in

Chapter 30 on Congestive Heart Failure the second factor mitral valve deformity will be discussed in Chapter 26 on Valvular Disease The third factor pulmonary embolism in its relationship to the heart will be discussed in the present chapter under the heading *the acute cor pulmonale* The fourth factor chronic pulmonary disease if extensive and prolonged enough gives rise to a cardiac condition which used to be called the emphysema heart but which along with the cardiac effect from the fifth sixth and seventh factors namely pneumoconiosis marked thoracic deformity and pulmonary endarteritis obliterans will be discussed below under the far superior designation *chronic pulmonary heart disease or the chronic cor pulmonale*

**Incidence** This condition—cor pulmonale or pulmonary heart disease—is an important one, though variable in incidence in different parts of the world It has been considerably neglected and is probably more common than most statistical studies at present indicate especially since it occurs so often in older people who are not frequently seen in general hospitals which treat acute conditions In New England its chronic form was noted 21 times (0.9 per cent) in 2,314 cases of organic heart disease (White and Jones 1928) but in certain places like Vienna (Erdheim personal communication 1929) and Cleveland (Scott 1941) it is either more common or better recognized Scott noted it in 6.8 per cent of 790 cases who died of heart disease in Cleveland Two groups of cases of chronic cor pulmonale studied at autopsy have been recently reported 60 by Spain and Handler in 1946 and 42 by Spatt and Grayzel in 1948 Of 123 collected cases analyzed by Sodeman (1948) 75 were associated with emphysema 14 with bronchial asthma 13 with silicosis 5 of which had also tuberculosis 9 others with tuberculosis 7 with bronchiectasis and 1 each with kyphoscoliosis pulmonary arteriosclerosis pulmonary fibrosis and schistosomiasis The incidence of the acute form is more common than was previously recognized being found in about 10 per cent of cases of acute pulmonary embolism but is probably present in additional cases though masked by other signs e.g. coronary insufficiency In slight degree it is not uncommon in high degree it appears to be rather rare

### ACUTE AND SUBACUTE COR PULMONALE

**Etiology Cause** Sudden massive obstruction of the pulmonary circulation sufficient to cause dilatation of the right ventricle gives rise to the condition which we have called *acute cor pulmonale* (McGinn and White 1935) The cause of such sudden massive obstruction of the pulmonary circulation is in the great majority of cases extensive pulmonary embolism originating from systemic venous thrombosis usually in the leg veins Conceivably a large embolus may also come from the right atrium but this is much less common as is likewise embolism from pelvic and abdominal veins Sudden perforation of an aortic aneurysm into the pulmonary artery can raise the pulmonary arterial pressure so abruptly that doubtless acute dilatation of the right ventricle antedates the inevitable death that ensues Also an acute compression of

the lungs by a sudden increase of a herniation of the abdominal contents through the diaphragm has been reported as a cause of the acute cor pulmonale (McGinn and Spear 1941), as has likewise acute spontaneous mediastinal emphysema (Klein 1947) Pneumonia and other pulmonary infections do not give rise to the acute cor pulmonale

*Age* The acute cor pulmonale is found in the great majority of cases in older persons that is in just those most subject to pulmonary embolism it is rare under 35 years of age

*Sex* Both sexes are about equally affected

*Predisposing factors* By far the most important predisposing factor is systemic venous thrombosis in the deep veins of the calf leading to involvement of the femoral veins or in the long saphenous veins whence multiple and often lengthy emboli are carried to the lungs favoring such thrombosis are stasis and phlebitis in individuals who have had a surgical operation (especially an abdominal or pelvic operation) or an accident or leg injury or any prolonged illness within a few weeks of the time of the occurrence of the pulmonary embolism Flabby musculature a prolonged cramped position especially seated with pressure under the knees and poor local circulation in the legs increase the likelihood of a venous thrombosis and pulmonary embolism under the conditions just mentioned

*Pathology* The only characteristic pathologic findings in the case of the acute cor pulmonale are dilatation of the pulmonary artery dilatation of the right ventricle and obstruction of the pulmonary artery or arteries usually by a single coiled massive embolic thrombus but sometimes by multiple emboli There must be a sudden blocking of at least 60 per cent of the pulmonary arterial circulation before the normal right ventricle dilates appreciably to effect this there must be either a large rider embolus at the bifurcation of the pulmonary artery or at least two large emboli one in each lung

There may or may not be congestive heart failure complicating the right ventricular dilatation At autopsy there may be little or nothing found wrong with the right heart because of the possibility of rapid subsidence of the functional cardiac dilatation especially if death has resulted finally from a state of vascular shock

Careful search at postmortem examination will almost always reveal extensive thrombosis in a long leg vein most often the superficial femoral or the saphenous which is frequently not evident during life

*Symptoms* There are no particular symptoms of the acute cor pulmonale per se except that some of the substernal oppression that attends the acute pulmonary embolism or resulting coronary insufficiency in an older person may possibly be attributed to the acute cardiac dilatation Any other symptoms are likely to be masked by the severe symptoms from the pulmonary embolism itself the state of shock sudden air hunger oppression in the chest cough weakness and sometimes syncope Substernal oppression due to a complicating angina pectoris or even to a secondary acute myocardial infarction occasionally appears Later symptoms if there is survival for twelve hours or more

may include epigastric discomfort from liver engorgement secondary to heart failure and fever and pleuritic pain due to the pulmonary infarction which is not at first evident

**Signs** Signs of the acute cor pulmonale include evidence of increase in size of the right ventricle of dilatation of the pulmonary artery and sometimes of failure of the right heart. Such signs may be transient or modified because of the coincident occurrence of coronary insufficiency or of vasomotor shock which reduces markedly the return of blood to the right heart and so prevents much dilatation thereof.

Characteristic signs related to the pulmonary artery dilatation that have been reported are forceful pulsation of the pulmonary artery evident both by inspection and by palpation along with increased percussion dullness at the left upper border of the heart, marked accentuation of the pulmonary second sound, a loud blowing pulmonary systolic murmur and a to and fro friction rub over the pulmonary artery very superficial and probably due to the pressure of the bulging artery and infundibulum against the pericardium underlying the sternum.

Signs indicative of right ventricular dilatation and failure include increased percussion dullness, diastolic gallop rhythm at the lower end of the sternum and engorgement of the neck veins with or without pulsation. There may even be some engorgement of the liver.

An interesting and important finding is that of an abnormal electrocardiogram which is characteristic and apparently pathognomonic. An S wave develops in Lead 1, the T wave in Lead 2 tends to be low or inverted, a Q wave develops in Lead 3 or is increased in amplitude, the T wave in Lead 3 is quite deeply inverted, and in the precordial leads over the right ventricle, in particular V<sub>1</sub> and V<sub>2</sub> but also at times V<sub>4</sub>, the T waves are flattened or more often inverted (Figure 99). These electrocardiographic changes come and go rather quickly along with changes in the condition of the patient; they are for the most part attributable to the acute dilatation of the right ventricle and not so much to anoxemia secondary to the pulmonary embolism itself. However, they are often masked or replaced in older patients with important degrees of coronary heart disease by patterns of coronary insufficiency or of myocardial infarction.

It is important to note that most instances of pulmonary embolism are not attended by the acute cor pulmonale chiefly because the obstruction of the pulmonary circulation is not of high enough degree; hence in only a minority of cases of pulmonary embolism should one expect to find the characteristic electrocardiogram. It was present in variable degree in 33 out of a series of 92 patients recently studied by the author but well marked in less than half of these, making a total of about 10 per cent of the entire series (Murnaghad, McGinn and White, 1943). There are therefore normal electrocardiograms in a large percentage of cases of pulmonary embolism although some have abnormal records due to pre-existing heart disease (especially coronary) further affected by the strain of the new vascular accident and in still others there are

suggestions of a slight degree of the acute cor pulmonale with or without underlying heart disease. It is of further interest to note as we have found and as has been pointed out by Currens (1942) that myocardial infarction may be precipitated by the strain and anoxemia secondary to pulmonary embolism

Lead

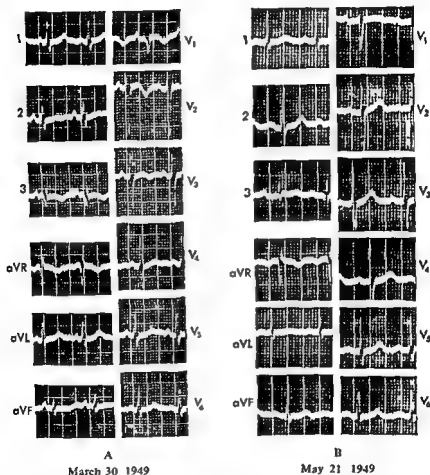


FIG 99 Electrocardiograms in a case of acute cor pulmonale female age 65 (A) Bipolar limb leads 1 2 and 3 unipolar limb leads aVR aVL, and aVF and six precordial leads V to V inclusive (B) Same several weeks after operation with removal of clot from leg vein Time = 0.04 and 0.20 second amplitude 1 mm = 0.10 mv

especially in older persons with less adequate coronary circulations. If such an infarct is in the posterior wall the electrocardiographic pattern may be at first confused with that of the acute cor pulmonale or the two may be superimposed as may also be the patterns of anterior myocardial infarction and the acute cor pulmonale. Even without actual infarction a temporary state of myocardial anoxia may alter the electrocardiogram but it will not produce



the pattern of the acute cor pulmonale. It is always important to explore the precordium electrocardiographically in the second and third positions overlying the right ventricle in the search for abnormality that is flattening or inversion of the *T* waves characteristic of the acute cor pulmonale.

Roentgen ray study of the acute cor pulmonale has not yet been adequately carried out in large part because of the very serious and transient nature of the fulminating illness but in rare cases cardiac dilatation has been noted. With acute pulmonary embolism the diaphragm on the affected side tends to be elevated but the infarction itself may not be evident for twenty-four hours or more and in some cases with good collateral circulation pulmonary embolism is not followed by infarction.

In the acute cor pulmonale the pulse is usually rapid and regular the arterial pressure is low and the venous pressure is often high.

*Pulmonary embolism* either with or without the acute cor pulmonale is often wrongly diagnosed or missed entirely. It should always be thought of when there recur at intervals of days to weeks unexplained episodes of chest discomfort, dyspnea, tachycardia, fever or blood spitting. Frequently only one of these symptoms is present although as a rule one finds an elevation of temperature, pulse rate and respiratory rate together the latter two out of proportion to the height of the fever. Pulmonary embolism will be discussed more fully in Chapter 28.

**Course and prognosis.** The course and prognosis of the acute cor pulmonale are extremely variable. Many cases die quickly more often from the state of shock incidental to the pulmonary embolism than from right heart failure. In many cases the condition is probably very transient lasting but a few hours at most and thus accounting for its neglect in the past or confusion with other conditions because of lack of time for study. A few cases show the condition for several days prior to recovery or to death from another pulmonary embolus. Doubtless in many cases the acute cor pulmonale is but slight and can be recognized only by very careful study.

**Complications.** The chief complications of the acute cor pulmonale are vasomotor shock which may abolish the cardiac dilatation, recurrent pulmonary embolism which is not uncommon and is likely to end fatally, myocardial ischemia or actual infarction particularly in cases with serious coronary artery disease already and congestive heart failure. Massive pulmonary embolism with resulting strain on the right ventricle causing dilatation and failure may itself complicate chronic heart disease and produce a grave condition that not infrequently terminates fatally but the immediate significance of which is often misunderstood; this is particularly true of severe mitral stenosis and of hypertensive or coronary heart disease with congestive failure. The commonest complication of mitral stenosis and of congestive heart failure is pulmonary embolism and an occasional complication of acute myocardial infarction (from coronary thrombosis) during convalescence is pulmonary embolism which has often been wrongly diagnosed as a new attack of coronary occlusion.

**Treatment** Therapy of the acute cor pulmonale includes absolute rest with head elevated (unless a state of shock supervenes) morphine  $\frac{1}{4}$  gr (0.015 gm) subcutaneously and oxygen inhalation (by tent). It is advisable to give digitalis in full dosage if the right heart fails: digitoxin 0.5 mg intravenously or by mouth repeated in 3 hours and again if necessary, or digoxin 0.8 mg intravenously repeated in 3 hours or digitalis leaf in solution 0.5 gm intravenously repeated in 3 hours. Pulmonary embolectomy introduced many years ago (Trendelenburg 1908) and carried out in a few cases proved to be an impracticable measure and as a rule unsuccessful because the emboli are so often multiple or split and because the operation itself is so hazardous. Papaverine hydrochloride has also been recommended for the treatment of acute cases in the dosage of 0.1 to 0.2 gm but its use is in general disappointing.

*It is even more important in treatment inasmuch as recovery is likely from the damage already done to search as soon as possible for the thrombosed vein in the leg which has been responsible for the massive pulmonary embolus which in turn has caused the acute cor pulmonale since life hangs in the balance from the threat of another and quite possibly fatal embolus.* The most careful physical examination may fail to reveal the thrombosed vein; contrast (Diodrast) roentgen ray study may show it readily but it is also unreliable and may itself induce thrombosis (see Chapter 28). Ligation of the offending or threatening veins of one or of both legs is often necessary to save lives. The use of heparin intravenously by constant drip though often helpful is not always adequate and may delay essential surgery.

**Differential diagnosis** The three conditions that are very likely to be confused with the acute cor pulmonale are (1) acute coronary occlusion with rapid failure of the left ventricle and pulmonary vascular congestion secondary thereto, (2) congestive heart failure complicating heart disease and attended by rales at the lung bases which may also result from bilateral pulmonary infarcts (quite commonly occurring at both lung bases and not infrequently concealed behind congestive hydrothorax) and (3) pulmonary infection also attended by rales in the lungs and not uncommonly complicating heart disease. A careful history past and present and the electrocardiogram usually distinguish these conditions but the greatest difficulty arises when two or all three of them occur simultaneously in the same patient. There are two other acute thoracic episodes that although much less common need to be thought of and ruled out when pulmonary embolism is being diagnosed: the first namely spontaneous pneumothorax is more frequent and easy to identify; the second *spontaneous mediastinal emphysema* a related condition is rare and not always clear; it is best diagnosed by the combination of substernal pain, a curious crunching sound over the heart in systole, roentgen ray evidence of air in the mediastinum and sometimes an escape of air into the subcutaneous tissues of the neck. (Hamman 1939)

## COR PULMONALE (PULMONARY HEART DISEASE)

**Etiology Cause** The cause of the condition called chronic pulmonary heart disease is chronically increased resistance in the pulmonary circulation due commonly to the narrowing of its arterioles and capillary bed and not the result of left heart failure mitral stenosis or congenital heart disease. The most pronounced and characteristic degree of the chronic cor pulmonale has been that associated with *silicosis* extensive pulmonary and pleural fibrosis and the rare pulmonary endarteritis obliterans. In lesser degrees the chronic cor pulmonale may result from marked pulmonary emphysema tracheal or bronchial stenosis pulmonary collapse or, in excessively rare cases in infancy failure of the alveoli to develop chronic inflammatory conditions of lung parenchyma mechanical factors resulting from chest deformities pulmonary arteriovenous communications (fistulae), congenital or acquired and other intrathoracic conditions. Infrequently permanent and extensive obstruction of the blood flow in the major pulmonary arterial trunks by large fibrosed thrombi originating as pulmonary emboli from the acute effects of which the patient has recovered is the cause of the chronic cor pulmonale and is likely to be overlooked clinically. Rarely pressure on and obstruction of the pulmonary artery by a syphilitic aortic aneurysm (Garvin and Siegel 1939) may be to blame.

Primary endarteritis obliterans of the pulmonary arteries noted first in several cases in the nineteenth century is generally of unknown cause but in rare cases it has been ascribed to syphilis (Ayerza 1901 Arrillaga 1912). Because of the deep cyanosis that has been seen in a few cases of this type the patients have been sometimes called black cardiacs but undoubtedly the major part of the cyanosis in these black cardiacs is due to the primary pulmonary disease which prevents the oxygenation of the blood and not to the secondary heart disease although of course, right heart failure with resulting systemic venous stasis accentuates the cyanosis (see Chapter 4). Clinically the effects on the heart of severe chronic pulmonary disease and of pulmonary endarteritis obliterans are much the same and they will be discussed together.

**Age** The heart disease that follows chronic pulmonary lesions occurs mostly in older persons. Of the twenty-one cases of White and Jones series all but four were more than 50 years old and thirteen were over 60 years of age. In Scott's series of fifty autopsied cases (Scott and Garvin 1941) thirty five were over 50 years old and sixteen over 60. The age incidence of primary pulmonary endarteritis is younger the condition being found mostly in young and middle aged men, the youngest case that I have encountered was a boy 11 years old at death.

**Sex** With respect to the cor pulmonale males are much in the majority as might be expected in view of their well known greater incidence of marked emphysema and pneumoconiosis (silicosis anthracosis asbestosis). Of 25 cases of chronic cor pulmonale of high degree found among 4 000 autopsies

at the Massachusetts General Hospital in the ten year period of 1932 to 1942 20 were male and only 5 were female (White personal analysis in 1942) in Scott's series of 50 cases, 48 were male and only 2 were female

*Predisposing factors* Severe climate poverty malnutrition and hereditary influences are factors which favor the occurrence of chronic pulmonary disease and thoracic deformities responsible for the chronic cor pulmonale but one of the most common predisposing factors of all is pneumoconiosis (especially anthracosis and silicosis) an industrial disease among coal miners and stone workers The coal or stone dust may saturate the lungs in a very few years to cause marked fibrosis and obliteration of many small arteries in the lungs tuberculosis and pneumonia are the common causes of death in these cases but a few succumb to heart failure, with improvement in industrial hygiene this hazard is lessening

*Pathology* The chronic cor pulmonale or pulmonary heart disease consists primarily of enlargement of the right ventricle (Figure 100 page 508) and of the pulmonary artery and secondarily of enlargement of the right atrium The increase in size of the right ventricle is due at first to hypertrophy as in the case of the left ventricular enlargement in systemic hypertension later as the heart fails dilatation of the right ventricle appears with relative tricuspid insufficiency and right atrial dilatation The essential lesion is that of hypertrophy of the individual muscle cells of the right ventricle Such changes as fibrosis fatty degeneration and fatty infiltration are associated with certain other conditions namely coronary disease anemia and obesity Failure when it comes is attended by dilatation due to muscular fatigue and not to degenerative changes unless there are complications Endocarditis and pericarditis occur only as rare and incidental complications in pulmonary heart disease

The right ventricle may be but slightly hypertrophied in the milder cases adding but little to the heart weight escaping clinical observation and passing notice sometimes even at postmortem examination Usually the enlargement is considerable and in rare cases it may be very great so that the right ventricle is as large as or larger than the left ventricle and the blunt apex of the heart is made up in large part by the right ventricle (see Figure 101 as an example of marked right ventricular enlargement)

The pulmonary artery and its branches may show areas of atheroma of varying number and size and some narrowing of the smaller arteries when the blood pressure in the pulmonary circulation is much elevated which happens in some cases of chronic pulmonary disease as it does in chronic mitral stenosis There is a different finding however in the case of pulmonary endarteritis obliterans the rarer pulmonary cause of the chronic cor pulmonale here one finds an actual hyperplasia of varying degree of the endothelium of the smaller arteries and arterioles in extreme cases almost a complete arterial obliteration In a few cases the treponemata of syphilis are reported to have been found in these endothelial lesions in most cases the cause is still unknown The left ventricle in the case of chronic pulmonary disease is not

primarily affected. It may, however, as in mitral stenosis be rather smaller than usual this finding has probably given rise to the erroneous idea that chronic pulmonary disease and emphysema always spare the heart and result in cardiac hypoplasia

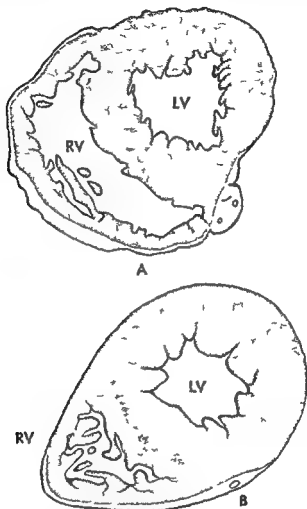


FIG 100 Drawings showing cross sections of (A) a dilated cor pulmonale and of (B) a normal heart at a level two thirds of the distance from base to apex of the ventricles. These cross sections are of natural size. RV = right ventricle. LV = left ventricle.

In the case of silicosis two morphologic processes have been described which evoke vascular changes in the pulmonary circulation (1) direct encroachment on the vascular wall by nodules or nodular masses and (2) infiltration of the vascular wall by dust bearing and pigment bearing granulation tissue (Geever 1947)

A very rare bizarre finding as a cause of the chronic cor pulmonale in infancy is failure of the lung alveoli normally to open up at birth. This results in

an extremely difficult bronchiolar respiration endarteritis marked enlargement of the right ventricle and early death within the first year (T B Mallory personal communication 1942) A rare cause of subacute cor pulmonale is a gradual vascular obliteration by carcinomatous emboli (Mason 1940)

**Symptoms** The chronic cor pulmonale produces symptoms only when it begins to fail Symptoms due to the chronic underlying pulmonary disease namely dyspnea cough and weakness have often been wrongly interpreted as those of early failure in pulmonary heart disease this error was made in the first edition of this book Actually symptoms of the heart failure are other than pulmonary and are due to congestion of liver gastrointestinal tract and dependent parts of the body Pain except in the congested liver, and palpitation are rare and not characteristic

**Signs** There may be little or no evidence of the chronic cor pulmonale itself because it so often is concealed by the underlying pulmonary condition but when the characteristic signs of marked chronic pulmonary fibrosis with emphysema are present one may rest assured that the heart is at least somewhat affected although it may still be competent A brief summary will first be given of the typical signs of advanced pulmonary fibrosis with emphysema and then the additional signs of cardiac involvement due to that condition

The signs of marked pulmonary fibrosis with emphysema are (1) cyanosis of varying degree often considerable and sometimes as intense as in the *maladie bleue* of congenital heart disease (2) clubbing of the fingers and toes (3) polycythemia the red blood cells being increased to 6 or 7 millions per cubic millimeter (4) lowered oxygen saturation of the arterial blood (5) restricted respiratory movements with emphysematous or asthmatic breathing (expiration prolonged and forceful) (6) frequent scattered squeaking or groaning pulmonary rales (7) low position of diaphragm with restricted respiratory movements very evident fluoroscopically (8) abnormally thickset or barrel shaped chest and (9) low vital capacity Most of these signs are also found in the cyanotic type of congenital heart disease and also except for the constant cyanosis and rales in long time residents at very high altitudes (over 12 000 feet or 4 000 meters)

The cardiac signs are those due to enlargement of the right ventricle and to a complicating failure when it appears Cardiac arrhythmia is uncommonly found There is frequently a pulmonary systolic murmur and the pulmonary second sound is usually accentuated The pulmonary arterial pressure is elevated to double or more the normal pressure (e.g. 50 or 60 mm mercury instead of 25) when tested by intracardiac catheterization The systemic blood pressure is as a rule low at about 100 to 110 mm systolic and 70 to 80 mm diastolic

The signs of failure are primarily those of failure of the right ventricle consisting of engorgement of the great veins including the jugular veins with the development of a jugular venous pulse in the upright and semiupright posture liver enlargement and tenderness ascites and edema of the legs Pulmonary signs are wholly those of the underlying pulmonary disease

The right ventricular enlargement is often made out with much difficulty especially on physical examination. There are three reasons for this difficulty in the first place, the right ventricle being anteriorly placed shows relatively less evidence of enlargement than does the left ventricle which increases downward and to the left as well as backward, secondly the low level of the diaphragm so often found in chronic pulmonary disease gives a deceptive small cardiac appearance (a drop heart) even when the heart is somewhat enlarged and thirdly the pulmonary emphysema, by making the thorax hyperresonant often prevents satisfactory percussion for the determination of the heart borders and even interferes with auscultation. Thus unless great care is exerted and electrocardiograph and roentgen ray are brought to one's assistance the enlargement of the chronic cor pulmonale may easily escape notice even with all this help the condition may be discovered only at post mortem examination. Electrocardiography shows right ventricular preponderance (Figure 101) unless there is also present left ventricular enlargement from some factor of strain (systemic hypertension aortic valve disease or myocardial infarction) in the same heart. The right ventricular preponderance pattern includes abnormal right axis deviation in the limb leads and especially higher peaks of the *R* waves in the precordial leads over the right ventricle (often with depressed or inverted *T* waves) and prominent *S* waves over the left ventricle. Roentgen ray study may or may not clearly show the right ventricular enlargement (Figure 102 see page 512), the view of the heart shadow in the anterior oblique positions is especially helpful in revealing the forward bulging of the right ventricle not made out in the anteroposterior position. Furthermore fluoroscopy sometimes shows dynamic dilatation of the pulmonary artery which may be marked especially in the case of pulmonary endarteritis obliterans. In this last named condition the lung fields have been noted as abnormally clear but as a rule the lung fields are very abnormal due to the underlying pulmonary disease silicosis, or chest deformity.

**Course and prognosis.** Pulmonary heart disease or the chronic cor pulmonale begins very gradually and insidiously usually in the long course of severe chronic bronchitis and emphysema or silicosis and years may elapse after it has been found before failure becomes marked. Its course and prognosis are so bound up with those of the pulmonary condition that the heart trouble must always be considered with the lung disease. Pulmonary infections especially pneumonia and phthisis have in the past usually caused death in these cases but many years of a careful life of moderate activity may elapse before death comes. It is probable that the limitations enforced by the pulmonary trouble protect the heart from excessive fatigue. Death from congestive heart failure in such patients occurs rarely.

The prognosis of cases with pulmonary endarteritis obliterans is less favorable than that of cases with chronic pulmonary fibrosis death coming from cardiac failure in the course of months to a few years at best after cyanosis has become apparent.

**Complications.** The two important complications heart failure either right

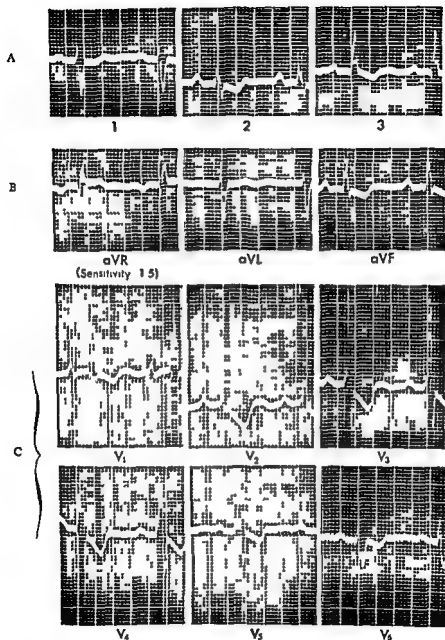


FIG 101 Electrocardiogram in a case of chronic cor pulmonale male age 30 (A) Bipolar limb leads 1 2 and 3 (B) unipolar limb leads aVR aVL and aVF (C) six precordial leads V<sub>1</sub> to V<sub>6</sub> inclusive Note the marked right axis deviation in the limb leads and the very high R and inverted T waves in the precordial leads V<sub>1</sub> to V<sub>3</sub> over the right ventricle Time — 0.04 and II 20 second amplitude 1.5 mm = 0.15 mv





FIG 10. Roentgenograms in two cases of the chronic cor pulmonale due to pulmonary endarteritis obliterans and pulmonary fibrosis (A) Roentgenogram showing increased heart (right ventricular) size and prominence of pulmonary artery. Boy age 10 who showed at autopsy a year later very extensive pulmonary endarteritis obliterans of unknown cause (B) Roentgenogram showing extensive pulmonary fibrosis and chronic cor pulmonale in HSG male age 49

sided or incidentally left sided and respiratory infections have been discussed above. Other types of heart disease may be associated with the chronic cor pulmonale, but only one coronary heart disease occurs with much frequency. Coronary heart disease is present in about half the cases, probably because of the advanced age of the majority of the patients.

**Treatment** The treatment of pulmonary heart disease consists in the therapy both of heart failure when present and of the pulmonary disease itself, but much more so of the latter since heart failure is rare in these patients. The usual therapy of congestive failure, if clearly present as shown by engorged liver, leg edema and increased jugular pulse, should be carried out (but not for dyspnea or cyanosis per se); rest in bed, digitalis, diuretics and symptomatic treatment as needed. Oxygen inhalation may prove to be especially helpful because of the pulmonary disease.

A therapeutic test with digitalis in cases of chronic bronchitis and emphysema is often helpful, since heart weakness is easily masked by the pulmonary condition. When signs of right heart weakness are thereby decreased, we have confirmatory evidence of the chronic cor pulmonale or of a secondary effect of coincidental left heart weakness. Careful differentiation between these two fundamental conditions is essential and will be discussed at length in Part IV. When however dyspnea, cough and cyanosis are appreciably decreased by saturation of the patient with digitalis, we have evidence only of left ventricular weakness and failure and not of the chronic cor pulmonale. If in either case there has been benefit by digitalis, its administration should thereafter constantly be maintained by daily fractions of the drug, and in cases of considerable right ventricular enlargement it is conceivable that regular fractions of digitalis may help to retard the onset of heart failure in the first place.

Care to avoid respiratory infections, the treatment of the pulmonary condition already present, the avoidance of fatigue, residence in a more favorable (drier) climate and not at high altitudes, and symptomatic therapy, especially the use of penicillin and oxygen as needed, will have a favorable influence on the course of pulmonary heart disease.

If syphilis is found present in rare cases of pulmonary endarteritis obliterans, specific therapy should be instituted with care, as outlined for syphilitic aortitis in Chapter 16.

Advances in thoracic surgery in the correction of chest deformities and pulmonary disease afford some hope for the future eradication of underlying causes of the chronic cor pulmonale in a few cases, even perhaps the removal of extensive thrombi, more or less organized from the pulmonary artery itself or from its chief branches in rare subacute or chronic cases when the responsible factor is obviously embolic thrombosis.

**Differential diagnosis** There are two conditions from which it is often difficult to distinguish pulmonary heart disease: (1) the pulmonary disease itself, and (2) congenital heart disease without characteristic murmurs (as in some cases of the tetralogy of Fallot, which consists of pulmonary stenosis

interventricular septal defect, dextroposition of the aorta and enlarged right ventricle) The presence of the emphysema the absence of any history of heart trouble or cyanosis in youth and the lesser degree of abnormality of the heart as determined by various methods of examination help to distinguish the chronic cor pulmonale from congenital heart disease though it is to be noted that pulmonary arteriolar disease and emphysema may themselves be important complications of congenital heart disease (the *maladie bleue*) The finding of right ventricular enlargement by roentgen ray and electrocardiogram the favorable response to the therapeutic test with digitalis and indeed the very presence of marked chronic emphysema point to pulmonary heart disease as a complication of emphysema Pulmonary endarteritis obliterans is found in younger individuals without pulmonary disease itself is sometimes attended by intense cyanosis (the *black cardiacs*) and has usually a rapid downhill course Mitral stenosis may in rare cases simulate pulmonary heart disease when the pulmonary vascular congestion is considerable and the right heart begins to fail but careful study, particularly the finding of the characteristic mitral diastolic murmur should clearly distinguish the two conditions

### BIBLIOGRAPHY

#### PULMONARY HEART DISEASE—COR PULMONALE ACUTE AND CHRONIC PULMONARY HYPERTENSION

SEE ALSO REFERENCES UNDER CHAPTERS 3 SYMPTOMS 4 SIGNS  
AND 28 VASCULAR DISEASE

#### Acute Cor Pulmonale

- Brill I C and Robertson T D "Subacute Cor Pulmonale" *Arch Int Med* 1947 LX 1043
- Churchill E D "The Mechanism of Death in Massive Pulmonary Embolism With Comments on the Trendelenburg Operation" *Surg Gynec & Obst* 1934 LXI, 313
- Currens J "The Electrocardiogram in Pulmonary Embolism" *Proc Staff Meet Mass Clin* 1942 XVII 502
- Klein A "Spontaneous Mediastinal Emphysema with Acute Right Ventricular Strain" *Am Heart J* 1947 XXXIII 867
- McGinn S and Spear L M "Diaphragmatic Hernia Presenting the Clinical Picture of Acute Cor Pulmonale" *New England J Med* 1941 CCXXIV, 1014
- McGinn S and White P D "Acute Cor Pulmonale Resulting from Pulmonary Embolism. Its Clinical Recognition" *JAMA* 1935 CIV 1473
- Mack I Harris R and Katz L N "Acute Cor Pulmonale in the Absence of Pulmonary Embolism" *Am Heart J* 1950 XXXIX 664
- Masini V Biocca P and Sposito M "Patogenesi delle alterazioni elettrocardiografiche nel cuore polmonare acuto" *Cuore e circolo* 1949 XXXIII 277
- Mason D G "Subacute Cor Pulmonale" *Arch Int Med* 1940 LXVI 1771
- Murnaghan D McGinn S and White P D "Pulmonary Embolism With and Without the Acute Cor Pulmonale with Especial Reference to the Electrocardiogram" *Am Heart J* 1943 XXV 573
- Nystrom G., and Blalock A "Contributions to Technic of Pulmonary Embolotomy Experimental Study" *J Thoracic Surg* 1935 V 169
- Phillips F and Levine H D "A Critical Evaluation of Extremity and Precordial Electrocardiography in Acute Cor Pulmonale" *Am Heart J* 1950 XXXIX 705

- Trendelenburg F Ueber die operative Behandlung der Embolie der Lungenarterie"  
*Verhandl d deutsch Gesellsch f Chir* 1908 II 89
- White P D "The Acute Cor Pulmonale" *Ann Int Med* 1935 IX 115
- Pulmonary Embolism and Heart Disease *Am J M Sc* 1940 CC 577

### Chronic Cor Pulmonale

- Alexander H L Luten II and Kountz W B "The Effects on the Heart of Long  
 Standing Bronchial Asthma" *JAMA* 1927 LXXXVIII 882
- Arrilaga F C *Esclerosis secundaria de la arteria pulmonar y su cuadro clinico*  
 (cardiacos negros) Thesis No 2536 Buenos Aires 1912
- Ayerza L *Maladie d'Ayerza sclerose secondaire de l'artere pulmonaire (cardiaques*  
 noirs) *Semana med* Buenos Aires 1925 No 1 p 43
- (Abel Ayerza gave in an unpublished lecture in 1901 the first clinical description  
 of this condition later named after him)
- Baldwin E deF Cournand A and Richards D W Jr Pulmonary Insufficiency  
 II A Study of Thirty Nine Cases of Pulmonary Fibrosis *Medicine* 1949 XXVIII 1
- "III Study of the 122 Cases of Chronic Pulmonary Emphysema *Ibid* 201
- Bedford D E Aidaros S M and Gurgis B Bilharzial Heart Disease in Egypt  
 Cor Pulmonale Due to Bilharzial Pulmonary Endarteritis *Brit Heart J* 1946 VIII  
 87
- Borden C W Wilson R H Ebert R V and Wells H S Pulmonary Hypertension  
 in Chronic Pulmonary Emphysema *Am J Med* 1950 VIII 701
- Brenner O Pathology of Vessels of Pulmonary Circulation Parts IV *Arch Int Med*  
 1935 LVI 211 457 74 976 1189
- Carroll D Chronic Obstruction of Major Pulmonary Arteries *Am J Med* 1950  
 IX 175
- Castleman B and Bland II F Organized Emboli of the Tertiary Pulmonary Arteries  
 An Unusual Cause of Cor Pulmonale *Arch Path* 1946 XLII 581
- Chapman II M Dill II B and Graybiel A The Decrease in Functional Capacity  
 of the Lungs and Heart Resulting from Deformities of the Chest Pulmonocardiac  
 Failure *Medicine* 1939 XVIII 167
- Chavez I Recents progressi nella conoscenza della cardiopatia polmonare *Cuore e*  
*circola* 1949 XXXIII 225
- Coggin C B Griggs II E and Sulson W L The Heart in Pneumoconiosis *Am*  
*Heart J* 1938 XVI 411
- Cournand, A and Richards D W., Jr "Pulmonary Insufficiency I Discussion of a  
 Physiological Classification and Presentation of Clinical Tests" *Am Rev Tuberc*  
 1941 XLIV 26
- Garvin C F and Siegel M L "Cor Pulmonale Due to Obstruction of Pulmonary  
 Artery by Syphilitic Aortic Aneurysm" *Am J M Sc* 1939 CXCVIII 679
- Geever E F Pulmonary Vascular Lesions in Silicosis and Related Pathologic Changes  
*Am J M Sc* 1947 CCXIV 292
- Giroux L *Sclérose et atherome de l'artere pulmonaire Role des conditions mecaniques*  
 Thesis G Steinheil Paris 1910
- Horne C F and Warner C G "Distribution of Pulmonary and Bronchial Circulation  
 Experimental Study" *J Thoracic Surg* 1932 II 80
- Hormann J Die Bedeutung des Elektrokardiogramms insbesondere der Brustwanda  
 bleitungen für die Begutachtung der Silikose *Ztschr f Kreislauff* 1950 XXXIX  
 624
- Johnson J II Ferrer M I West J R and Cournand A "The Relation Between  
 Electrocardiographic Evidence of Right Ventricular Hypertrophy and Pulmonary  
 Arterial Pressure in Patients with Chronic Pulmonary Disease" *Circulation* 1950  
 I 536
- Kenawy M R "The Syndrome of Cardiopulmonary Schistosomiasis (Cor Pulmonale)"  
*Am Heart J* 1950 XXXIX 678
- Lenègre J and Maurice P La pression ventriculaire droite moyenne (P V D M) dans  
 certaines affections bronchopulmonaires chroniques" *Brit Heart J* 1948 X 81
- Litten M Ueber Verengerungen im Stromgebiet der Lungenarterie über deren Folgen

- und die Möglichkeit dieselben während das Lebens zu diagnostieren zugleich ein Beitrag zur Lehre von der ungleichzeitigen Contraction beider Herzkammern" *Berlin klin Wchnschr* 1882 XIX 425 and 443
- McMichael J Pulmonary Heart Disease Acute and Chronic *Brit Heart J* 1948 X 80
- Scott R W and Garvin C F Cor Pulmonale Observations in Fifty Autopsied Cases *Am Heart J* 1941 XXII 56
- Smith A R Study of Granite Cutting and Granite Cutters in Vicinity of New York City *Am J Pub Health* 1934 XXIV 821
- Soderman W A Pulmonary Heart Disease *Dis of Chest* 1948 V 360
- Spain D M and Handler B J Chronic Cor Pulmonale Sixty Cases Studied at Necropsy *Arch Int Med* 1946 LXXVII 37
- Spatt S D and Grayzel D M "Cor Pulmonale Observations on Forty two Autopsied Patients *Am J Med* 1948 V 252
- Taquini A C Fasciolo J C Suarez J R E and Chrodi M Circulatory Adaptations in Ayerza's Syndrome—Black Cardiacs *Am Heart J* 1947 XXXIV 50
- Thomas A J Right Ventricular Hypertrophy in the Pneumoconiosis of Coalminers *Brit Heart J* 1951 XIII 1
- White P D and Jones T D "Heart Disease and Disorders in New England *Am Heart J* 1928 III 302

#### Spontaneous Mediastinal Emphysema

- Hamman L Spontaneous Mediastinal Emphysema *Bull Johns Hopkins Hosp* 1919 LXIV 1
- Klein A Spontaneous Mediastinal Emphysema with Acute Right Ventricular Strain *Am Heart J* 1947 XXXIII 867

---

## CHAPTER 21

---

# CORONARY HEART DISEASE ANGINA PECTORIS CORONARY THROMBOSIS AND MYOCARDIAL INFARCTION

---

**Introduction** For convenience and consistency a simple rearrangement has been introduced into this new edition whereby the former Chapter 31 on Coronary Insufficiency Including the Symptom Angina Pectoris has been for the most part incorporated into the present chapter where it best belongs<sup>1</sup> thus omitting considerable repetition and saving space and the short appendix on Atherosclerosis has been transferred appropriately to Chapters 26 and 28.

This chapter is one of the most important in the book and demands at the outset the consideration of basic definitions nomenclature and arrangement too often neglected or confused in the rapidly growing literature on the subject. In the first place coronary disease is not heart disease though it is often loosely and inaccurately designated as such. Strictly it does not even mean coronary artery disease since coronary veins form an important part of the coronary circulation common usage however and the fact that in the present state of our knowledge the coronary veins are not the site of any serious pathologic process justify the use of the term as synonymous with coronary arterial disease. Also since practically the totality of coronary arterial disease is atherosclerotic in type coronary atherosclerosis is implied when the term coronary disease is used without other qualification. The designations coronary insufficiency and coronary failure usually attended by the symptom angina pectoris and often leading to myocardial infarction are not strictly synonymous with coronary disease since other conditions such as syphilitic aortitis with a blocking of the coronary circulation at its origin may be the cause and since coronary disease even extensive in degree may be present without insufficiency of blood supply to the heart muscle.

The terms coronary occlusion and coronary thrombosis have been loosely used to indicate myocardial infarction but there should be a correction

<sup>1</sup> I am grateful to Dr. John Parkinson for his helpful advice in this respect.

of this common error To be sure myocardial infarction often results from acute coronary thrombosis or occlusion but the two designations should not be employed synonymously myocardial infarction may occur without actual complete coronary arterial thrombosis or occlusion and coronary occlusion may occur without myocardial infarction, if the process is slow in development or (and) the collateral circulation is adequate What has usually been meant clinically by the diagnosis of coronary thrombosis as an acute illness is myocardial infarction The terms coronary occlusion and coronary thrombosis are not strictly synonymous either although in acute processes they can be so considered for practical purposes, old calcareous occlusions of the coronary arteries may exist with never any symptoms therefrom and not even proof of past thrombosis

Finally the term coronary heart disease continues to be to my mind the best designation for the various effects of coronary arterial disease on the heart deleterious enough to cause symptoms or signs or postmortem evidence of more than trivial damage to the heart itself chiefly of course to the heart muscle Thus myocardial ischemia with angina pectoris or electrocardiographic abnormalities due to coronary disease acute myocardial infarction and old scars of similar origin are all included under this heading In the first two editions of this book acute coronary thrombosis with myocardial infarction was not considered as was the general custom in those days as a separate entity in a chapter by itself since it is but a phase of coronary heart disease New knowledge has confirmed the soundness of continuing this procedure in the third and fourth editions

**Historical** The earliest correlation of coronary disease with serious illness was made by Bonetus in 1700 in the second edition of his *Sepulchretum* when he described the case of a fat middle aged poet who succumbed in a few minutes after the onset of distress in breathing (which may have been angina pectoris) and who showed at autopsy calcified coronary vessels which were almost if not completely occluded Morgagni in 1761 was however unaware of the symptomatology of coronary disease and seven years later (1768) Heberden (quoted on page 538 of this chapter) was unaware that angina pectoris which he described so well was due to heart trouble It was Jenner a few years later (in 1772 as quoted by Parry 1799) who made that discovery Fothergill (1776) and Black (1794) published case reports of angina pectoris with ossified coronary arteries and the former also described myocardial scars

During the nineteenth century and until our own generation (Herrick 1912) astonishingly little advance was made in the clinical recognition of coronary heart disease despite the important contributions mostly anatomic of Weisert (1880) Cohnheim (1881) Ziegler (1881) Huber (1882) Leyden (1884) and Marie (1896)

The following quotation from Herrick's classical paper presents the earliest complete clinical description of sudden coronary occlusion Herrick recog-

nized even at the beginning that the clinical picture is often complex and variable a fact that has been re emphasized of late

Herrick J ■ Clinical Features of Sudden Obstruction of the Coronary Arteries  
*JAMA* 1912 LIX 2015

Obstruction of a coronary artery or of any of its large branches has long been regarded as a serious accident. Several events contributed toward the prevalence of the view that this condition was almost always suddenly fatal.

But there are reasons for believing that even large branches of the coronary arteries may be occluded—at time acutely occluded—without resulting death at least without death in the immediate future. Even the main trunk may at times be obstructed and the patient live. It is the object of this paper to present a few facts along this line and particularly to describe some of the clinical manifestations of sudden yet not immediately fatal cases of coronary obstruction.

The influence of the vessels of Thebesius is also not to be overlooked in this connection. compensatory circulation through these accessory channels may be of considerable importance in nourishing areas of heart muscle poorly supplied by sclerotic or obstructed arteries.

The clinical manifestations of coronary obstruction will evidently vary greatly depending on the size, location, and number of vessels occluded. No simple picture of the condition can therefore be drawn. All attempts at dividing these clinical manifestations into groups must be artificial and more or less imperfect. Yet such an attempt is not without value as it enables one the better to understand the gravity of an obstructive accident, to differentiate it from other conditions presenting somewhat similar symptoms, and to employ a more rational therapy that may to a slight extent at least be more efficient.

A study of cases of this type shows that nearly all are in men past the middle period of life. Previous attacks of angina have generally been experienced though as shown by my first case the fatal thrombosis may bring on the first seizure. The seizure is described by patients who have had previous experience with angina as of unusual severity and the pain persists much longer. In some instances there has been no definite radiation of the pain as to the neck or left arm though this may have been a feature of other anginal attacks and the pain as in these two cases may be referred to the lower sternal region or definitely to the upper abdomen. Cases with little or no pain have been described. Nausea and vomiting with belching of gas are common. There may be tympany. Ashy countenance, cold sweat, and feeble pulse complete the picture of collapse. The attention of the patient and the physician as well may therefore be strongly focussed on the abdomen and some serious abdominal accident be regarded as the cause of the sudden pain, nausea, collapse.

Cohnheim found that in dogs the pulse after obstruction was slow. This may be seen in the thrombotic obstruction of disease in man. In Hammer's case (1878) the pulse dropped from 80 to 8 per minute, the patient living thirty hours from the onset of the symptoms that marked the closure of the right coronary opening. A rapid pulse is frequently seen however. The pulse may be irregular. A striking feature has been its weakness. Blood pressure is low. The heart tones have been feeble—in fact often startlingly feeble.



Dyspnea and cyanosis have been variable  $\frac{1}{2}$  times much less than one would expect from the character of the accident and the quality of the heart's action. Rales dry and moist have been present in many cases.

General weakness has been marked in some cases in others not.

The occurrence of serofibrinous exudate over the area of myocardial softening with roughening of the pericardium has been noted in several instances. This may explain a later precordial distress as in Case 1. A fine pericardial friction therefore occurring several hours or a few days after the initial pain may be confirmatory evidence of coronary obstruction.

Death may be caused by rupture by sudden asystole or by gradual giving out of the weakened heart muscle.

Emphasis ought to be laid on the resemblance of some of these cases to surgical accidents.

If these cases are recognized the importance of absolute rest in bed for several days is clear. It would also seem to be far wiser to use digitalis, strophanthus or their congeners than to follow the routine practice of giving nitroglycerine or allied drugs.

**Incidence.** Extensive coronary arteriosclerosis is not only a very frequent and important cause of heart trouble near the end of the life cycle but it also cripples and kills often in the prime of life and sometimes even in youth. It is problematic whether the coronary sclerosis of senile life can ever be controlled but it is to be hoped and expected that some progress can be made in the prevention of such disease in persons who have not reached old age.

Coronary atheroma and sclerosis of slight to moderate degree are doubtless but part and parcel of the process of growing old. Not only is it difficult indeed impossible in the present stage of our knowledge to recognize the limits of the normal range anatomically as well as clinically at any particular age but even when the coronary arteries are markedly involved the heart itself may remain both structurally and functionally essentially normal. This is a very important but inadequately recognized fact. Of a series of 1000 consecutive postmortem examinations 371 cases (37.1 per cent) showed macroscopic coronary disease while of these 371 cases only 238 (64 per cent) showed any definite myocardial lesions (fatty change alone in 48 of them and fibrosis in the remaining 190) (Allan 1928). It is furthermore to be observed that limitation of blood supply to the heart by narrowed coronary vessels may limit cardiac action and reserve without actually causing structural lesions.

Coronary sclerosis as a cause of heart disease varies somewhat in its relative incidence in different parts of the world largely according to the frequency of such other causes as rheumatic heart disease, hypertension and syphilitic aortitis. It is of interest that although heart disease has been on the increase since 1930 this has largely been due to a rise in the incidence of coronary heart disease in contrast to other types of heart disease (Figure 103). In New England 37 per cent of a series of 2314 patients with organic heart disease were diagnosed as having some grade of coronary heart disease in about half of them uncomplicated and in the other half complicating other types of

heart disease mostly the hypertensive type (White and Jones 1928) A recent survey of 3 000 cardiac patients in New England showed a considerable increase of the relative incidence of coronary heart disease up to 48.5 per cent (White 1951)

In Clawson's series (1941) of 4 678 cardiac deaths among 30 265 autopsies there were 1 215 cases of coronary heart disease (30 per cent of the cardiac cases) three quarters of which were also hypertensive Statistics at present are not truly comparable for sometimes only those cases are recorded as

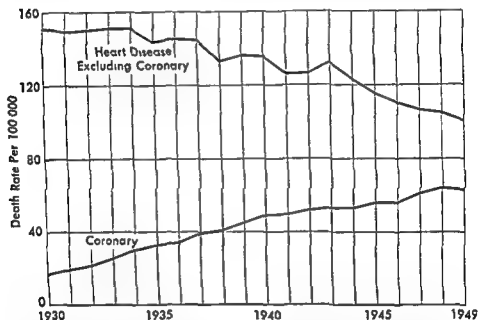


FIG 103 Annual age adjusted death rates of insured individuals from diseases of the coronary arteries as compared with other chronic diseases of the heart. Ages 1 to 74 years Metropolitan Life Insurance Company 1930-1949 (*Statistical Bulletin* Metropolitan Life Insurance Company New York City [January] 1950 XXXI 11)

coronary heart disease in which the coronary involvement is the primary cause of disability or death while sometimes all cases are so tabulated that show any suggestion of coronary involvement whatsoever We need many more studies than we possess at present to determine to what extent coronary disease including coronary thrombosis has been increasing if at all in the present generation Two representative studies of the few that are available are as follows Meakins and Eakin (1932) found that the percentage of incidence of coronary thrombosis with occlusion (slightly less than 1 per cent) among the autopsies at the Royal Victoria Hospital in Montreal in the five year period from 1926 to 1930 inclusive was actually less than that from 1896 to 1900 inclusive and Levy Bruenn and Kurtz (1934) reported that the autopsy diagnosis of coronary disease at the Presbyterian Hospital in New York City

increased from 17.8 per cent in the decade from 1910 to 1920 to but 30.4 per cent in the next decade while the cases with the clinical diagnosis of coronary disease jumped from 7 to 454. The autopsy diagnosis of coronary thrombosis and of myocardial infarction at the Massachusetts General Hospital rose rapidly in incidence among the total autopsies from rare cases in the middle 1920s to 13 to 14 per cent in 1940 and 1941 probably due in considerable part to more careful search by the pathologists (Wang et al 1948). It may be that coronary heart disease or its symptoms, in particular angina pectoris, are more common in this day and age, at any rate it is certain that the diagnosis is much more often made during life. Even young people with coronary heart disease are now being reported quite often the largest series being 866 in number 450 of whom were confirmed at autopsy aged 18 to 39 years in U.S.A. military service (Yater et al 1948).

**Etiology Cause** The reduction of the blood supply to the myocardium explains the deleterious effect of coronary disease on the heart. This blood supply is reduced by the narrowing or obstruction of the coronary arteries locally or generally a slight degree of abnormality of the coronary arteries may exist however without restriction of blood flow. Moreover other causes exist for a poor blood supply to the myocardium even when the coronary arteries themselves are normal severe anemia marked aortic stenosis or regurgitation extreme bradycardia extreme tachycardia marked temporary hypotension (as with vasodilatation in surgical shock) and blocking of the mouths of the coronary arteries by large vegetations on the aortic valve or by syphilitic aortitis.

Coronary disease may be of various types. In the normal evolution of the coronary circulation simple thickening of the elastic hyperplastic layer of the intima may occur so that in contrast to other arteries of the same size the intima may exceed the media in thickness doubtless due to the fact that these are the smallest vessels receiving blood under a high head of pressure (Wolkoff 1929) only if this change is marked is it to be considered as pathologic. A fibrotic thickening may also develop especially in certain areas. Dock (1946) reported the findings of a thicker coronary wall and relatively narrower lumen normally in the male than in the female infant.

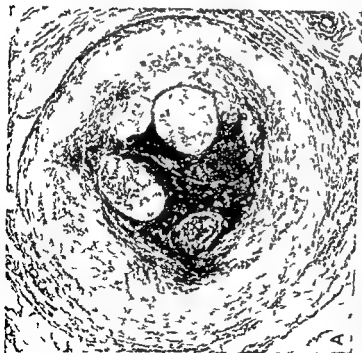
In the great majority of cases of coronary artery disease ordinary atheroma (αθήρη meal or porridge) is to blame this consists of softening the precursor of arteriosclerosis with yellowish fatty (cholesterol) areas in the endarterium. Fibrosis, thickening so-called cholesterol abscesses and calcification ensue and the arteries may become brittle, the abscesses sometimes break or give rise to ulcerations whereby thrombi may form. Hemorrhages from the rupture of minute vessels (vasa vasorum) in the vascularized atherosclerotic walls of the diseased coronary arteries are thought also to favor or to precipitate coronary thrombosis (Paterson 1936 1941). A tendency to either thrombosis on the one hand or to hemorrhage on the other as characteristic of cases of acute coronary occlusion has been suggested in the past but not confirmed. Reaction to atheroma is both fibrosis and especially in older decades calcifi-

cation and the formation of cholesterol abscesses (Leary 1935) See Figures 104 and 105

The cause of atheroma of the coronary arteries, as well as that of arterio sclerosis in general is still unknown Faulty cholesterol metabolism, local



FIG 104 Microphotographs of coronary arteries with moderate atherosclerosis (A) High power magnification of lipid cells underlying the endothelium and overlying collagenous bands of fibrous tissue (scarring from previous deposits of the sort) in a coronary artery of a man of 54 years X 280 (B) Microphotograph of coronary arteries in a youthful case of extensive coronary atherosclerosis X 30 times Man age 26 collapsed while removing a wheel from an automobile and died in a few minutes Note the almost complete obstruction of the descending branch of the left coronary artery by the extensive intimal fibrosis with necrosis in the deepest layer (crescentic in shape) just overlying the media and the blocking of the small remaining lumen by a fresh antemortem clot (stained black and roughly U-shaped) (kindness of Dr Timothy Leary Boston City Hospital Boston)



B

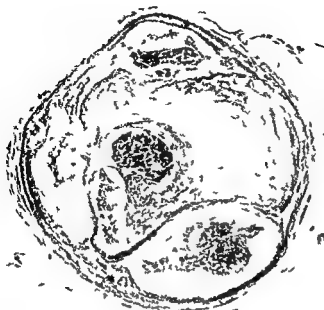


FIG 103 Microphotographs of cross sections of coronary arteries in two cases of extensive coronary atherosclerosis showing later developments  $\times 30$  times (A) Man age 53 who died suddenly at a railroad station he had had no illness and had worked continuously. Note almost complete obliteration of anterior descending branch of the left coronary artery with recanalization of an organizing thrombus in the old lumen. There is one new artery at the left and three veins above and to the right (B) Man age 62 found dead the day after strenuous work. Note the markedly fibrosed lumen of the anterior descending branch of the left coronary artery with four so-called "atheromatous abscesses (atherocheumata) one discharging into the small oval lumen of the artery in which there is a fresh antemortem thrombus (kindness of Dr Timothy Leary Boston City Hospital Boston)

arterial strain or overwork hypertension infection allergy endocrinopathy and heredity are among the many factors suggested but none has been proved or even consistently found. The frequent finding of a high blood cholesterol content in fasting cases of coronary heart disease especially in the young patients under 40 along with a low basal metabolic rate is in favor of a disturbance of fat metabolism at least as one factor. The suggestion of local overwork or strain is supported in the case of coronary atheroma by the finding that it is most common at the bend of the descending branch of the left coronary artery just below its mouth and that serious coronary sclerosis relatively is more common in hypertensive individuals than in persons with normal blood pressure. The hypertension antedating any evidence of coronary disease the frequency of coronary disease in myxedema and diabetes supports the idea of a factor of disturbed fat metabolism secondary to endocrinopathy and the factor of heredity is supported by the frequent finding of several members of a single family with serious coronary sclerosis. The combination of several etiologic factors is plausible.

An interesting presentation by Moreton (1948) of a possible mechanism based on the physicochemical introduction of coarse particulate matter containing fat (large lipid molecules) into the coronary artery wall where it acts as a foreign body illustrates a current viewpoint.

Considerable research is now in progress in an attempt to determine the responsibility of blood cholesterol and other lipids in the genesis of serious coronary atherosclerosis. Three varied types of investigation may be cited as examples of such research.

1 *Chemical* An investigation of 100 persons (97 males and 3 females) who had acute coronary occlusion before the age of 40 years (Gertler and Garn and associates 1950) have shown that more significant than the total cholesterol content of the blood which was found to be elevated in most cases was the ratio of such cholesterol to other phospholipids. This was considerably higher than normal. Incidentally the blood uric acid was also found to be on the high side and this figure added to the other two in the form of a quotient has proved of considerable interest.

In keeping with this chemical study Barr (1951) has found in another chemical study of the blood fractions in atherosclerotic cases a higher ratio than normal of *beta* lipoprotein which contains a larger amount of cholesterol in relation to phospholipids to *alpha* lipoprotein which contains much less cholesterol in relation to phospholipids.

2 *Physical* Research on the blood lipoproteins by the use of the ultracentrifuge has also proved to be of special interest. Gofman et al (1950) found appreciably more of a light molecule of cholesterol protein floated at a so-called SF 10 to 20 level in patients after recovery from acute myocardial infarction than in the case of normal controls. For example 95 per cent in males and 100 per cent in females as compared to 60 and 45 per cent respectively at the age of 40 to 50 years.

3 *Tissue culture* Finally Simms (1948) has tested the amount of lip-

lipanogens (precursors of visible fat) and of an inhibiting enzyme called antilipfanogen in the blood of normal and diseased individuals by determining the amount of fat taken up from the blood by tissue cultures. He has found that the ratio of antilipfanogen to lipfanogen, which is 1.0 in normal individuals is much reduced in cases of nephrosis and diabetes and moderately reduced in patients with coronary heart disease.

A comparison of the findings of these three different techniques—chemical, physical, and by tissue culture—is in progress.

It is of interest to point out that the foods which contain maximum amounts of cholesterol in order of content per average serving (not per weight) are brains, liver, sweetbread, scallops, oysters, eggs, lobster, crabs, beef, veal, pork, cheese, etc. By weight, eggs are second after brain.

On the other hand, it is also current opinion that the cholesterol that is deposited in the coronary artery wall may be produced in large part within the body itself, that is, that it may be of endogenous origin. It conceivably may be both. It seems very likely that the total caloric value of the diet may be more important than the food elements themselves inasmuch as cholesterol may quite possibly be produced richly on a solely carbohydrate diet if hearty enough (witness the cow). If an inadequate or barely adequate diet (in calories) is given, it is not so likely that cholesterol in large amount will be deposited in the coronary arterial intima whatever the food ingested may consist of, but that an excess diet with gain in weight may have such an effect more readily (?) if there is rich cholesterol intake. Here, however, we are dealing only with conjectures.

A different and rare type of coronary disease is that due to syphilis, here the media is primarily involved but later the intima too.

Still another type of coronary disease, and one that is relatively infrequent, is that due to *rheumatic* or *other nonsyphilitic infection*. The intima and media are involved and there may even result aneurysmal dilatation (mycotic aneurysms).

*Endarteritis obliterans* is a very rare cause of coronary artery disease; it is most often only a complication, being found in other vessels than the coronaries, mostly in the legs. It is itself of unknown origin, but the excessive use of tobacco has been suggested as an etiologic factor. Related to this and of obscure origin is an extensive disease of the whole coronary artery wall in infants (Stryker, 1946; Menten and Fetterman, 1948). *Periarteritis nodosa* may involve the coronary arteries at any age and has been noted to cause coronary thrombosis and myocardial infarction at even the early age of 1 year (Pickard et al., 1947).

The coronary arteries, healthy or relatively healthy themselves, may rarely be blocked by *emboli*, even of air, so that death or cardiac infarction may result, or they may be more or less occluded at their mouths by syphilitic aortitis or by aortic valve vegetations in bacterial endocarditis. The pressure of tumors and perhaps even of pericardial fluid and constricting adhesions may interfere with the coronary blood flow.

*Trauma* of the coronary arteries has been infrequently encountered as the result of pericardial paracentesis stab and gunshot wounds and unusual accidents Hemopericardium and death from tamponade generally follow such trauma

*Rupture* of a coronary artery may not only follow trauma but is a rare spontaneous occurrence as the result of a *dissecting aneurysm* extending from the aorta or limited to the coronary artery itself as a sequel to coronary thrombosis Coronary aneurysms themselves are rare they may be congenital mycotic embolic syphilitic or arteriosclerotic—a series of 47 cases collected from the literature (Scott 1948) showed 15 of the first 12 of the second 6 of the third 6 of the fourth while the remaining 8 were miscellaneous or unclassified

Finally *congenital abnormalities* of the coronary arteries may very rarely account for trouble when the cardiac activity is such that a single vessel or some other restriction of blood supply is incapable of maintaining a normal blood flow to the myocardium or when one of the coronary arteries arises from the pulmonary artery with resulting myocardial necrosis in the part of the heart supplied by this vessel Such an anomaly the left coronary artery coming off the pulmonary artery was responsible for left ventricular myocardial necrosis enlargement and failure and for attacks of distress on effort which were probably angina pectoris followed by early death in a four months old infant (Bland White and Garland 1933) Coronary arteriovenous aneurysms or fistulae occur very rarely I have encountered one such case in a boy of 9 years without disability who showed a continuous murmur at the right of the lower end of the sternum arousing a suspicion of coronary involvement which was found on surgical exploration (Paul Sweet and White 1949)

*Age* The age of occurrence of coronary disease and accordingly of myocardial changes due to coronary disease varies from youth to extreme old age, but it naturally increases with years Statistical studies of the age incidence of coronary disease are likely to be misleading because of the fact that slight atheromatous or atherosclerotic changes are frequently found in the coronary arteries on routine postmortem examination without their having any clinical importance whatsoever and hence not actually constituting disease from the clinical point of view and because a good many old persons with slight coronary insufficiency due to coronary disease do not trouble to seek medical advice since they consider their condition to be simply a part of old age as in fact it is Several studies in particular those by Wolkoff (1929) by Ehrlich and his associates (1931) and by Leary (1935) have shown that atheromatous changes may be seen in the coronary arteries as early as the first decade when they may still be retrogressive Atheroma and increase in thickness of the elastic hyperplastic layer of the intima are found frequently in the anterior descending branch of the left coronary artery in the second decade and regularly in all cases over forty years of age such changes are found later by about two decades in the right coronary artery and other large branches The age groups of 864 cases of coronary heart disease diagnosed clinically



in New England (White and Jones 1928) as compared with 1 346 recent cases (White 1951) have been reported as follows

Table 9

## AGE GROUPING OF CASES OF CORONARY HEART DISEASE

Clinical coronary heart disease		Group of 864 Cases Reported in 1928	Group of 1,346 Cases Reported in 1951
		Percentage	Percentage
	Under 40 years of age	0.2	3.8
	40 to 50 years of age	6.1	12.3
	50 to 60 years of age	22.7	26.5
	60 to 70 years of age	44.1	33.1
	Over 70 years of age	26.9	24.3
		93.7	83.9

This age grouping represents a cross section of the cases as they were seen by us the ages at onset of the disease would average a few years earlier as noted below

A series of 497 cases of angina pectoris gave the following age grouping at the onset of their disease (White Bland and Miskall 1943)

Angina pectoris (age at onset)	30 years of age and under	4 cases	0.8 per cent
	31 to 40 years of age	16 cases	3.2 per cent
	41 to 50 years of age	106 cases	21.4 per cent
	51 to 60 years of age	206 cases	41.4 per cent
	61 to 70 years of age	131 cases	26.4 per cent
	71 to 80 years of age	34 cases	6.8 per cent
	Over 80 years of age	0 cases	0 per cent

Our youngest case was 20 years old our oldest was 80 the average age at onset was 56.5 years

The age incidence of coronary thrombosis with cardiac infarction diagnosed clinically is much the same as that of angina pectoris. The age groups of 461 cases analyzed by Bland and White (unpublished data 1936) are as follows

Clinical coronary thrombosis with myocardial infarction (age at onset)	Below 30 years of age	3 cases	0.7 per cent
	30 to 40 years of age	16 cases	3.5 per cent
	40 to 50 years of age	80 cases	17.4 per cent
	50 to 60 years of age	169 cases	36.6 per cent
	60 to 70 years of age	142 cases	30.8 per cent
	70 to 80 years of age	47 cases	10.2 per cent
	Over 80 years of age	4 cases	0.9 per cent

Our youngest case was 22 years old our oldest 81 the average age at onset of the entire series of 461 cases was 56.2 years. Since the analysis of this series we have encountered in another series that of 100 cases under the age of 40, six patients all men under the age of 30 (Gertler, et al 1950). I have seen still a few other patients under 30 years old the youngest was a 22 year old soldier with xanthomatosis. Yater and his associates have reported 450 cases of men in military service who had fatal coronary heart disease as proved at autopsy between the ages of 18 and 39 years (Yater et al 1948). The youngest cases of atheromatous coronary thrombosis on record have been

a lad aged 12 years with diabetes (Shivelhood 1948) a girl aged 16 (MacDougall 1949) a boy 18 years old (Jamison and Hauser 1925) and a young woman of 19 (Evans and Graybiel 1948) One other case of progeria male aged 7½ died of coronary occlusion at the Massachusetts General Hospital (Talbot et al 1945)

And now very recently (1949) Gertler and Garn of our Massachusetts General Hospital coronary research group through the kindness of Drs J H Hamilton and C V Hawke have studied a large group of eunuchs and found among them a strikingly low incidence of coronary heart disease even in the older cases and also a very low blood cholesterol content

Coronary embolism though rare may occur at any age even in youth Two cases of cardiac infarction so caused under the age of 30 years have been reported by Parkinson and Bedford (1928) even in infancy cardiac infarction due to infectious embolism is on record (Schaps 1905) There are also two reports of paradoxical coronary embolism from a femoral vein thrombus in a man aged 35 years and in a woman aged 47 both without coronary disease (Saphur 1933 Jacoby et al 1934)

*Sex* The male sex is more often affected and to a more serious degree by coronary heart disease than is the female In a series of 200 clinical cases of cardiac infarction (Bland and White 1941) 168 (84 per cent) were male and 32 (16 per cent) were female while in a series of 83 postmortem cases of the same condition reported by Parkinson and Bedford (1928) 72 were male and 11 were female The ratio of males to females in Clawson's autopsied series of 1215 cases of coronary heart disease (1941) was 4.2 to 1 The most interesting and highly significant ratio of all has been in two separate groups of 100 patients each under the age of 40 years with coronary heart disease with or without myocardial infarction the first group reported by Glendy Levine and White in 1937 and the second group under recent study by our research team at the Massachusetts General Hospital there were 96 males and only 4 females in the first group and 97 males and 3 females in the second These findings would appear to be of great significance in the consideration of the etiology of coronary heart disease and demand further analysis *Why should the robust and apparently most masculine young male be particularly prone to this disease?* Is there a sex difference in the metabolism of fat or in its deposition? Does the greater thickness of the coronary artery wall in the male than in the female infant reported by Dock (1946) and by Minkowski (1947) play a role? Is it a part of the law of the animal kingdom whereby the male is more vulnerable than the female with a shorter life span (Hamilton 1948) by 4 or 5 years in the U.S.A. of recent years?

*Other etiologic factors* Race temperament social and economic status and occupation appear to have but slight bearing on the incidence of coronary heart disease At one time it was thought that coronary atherosclerosis was uncommon in the Negro but now increasing evidence thereof has been adduced by more adequate studies recent reports have been published by Hunter (1946) and Smith (1946) It is still stated that coronary thrombosis

is comparatively rare in the Chinese but similarly further studies thereof are needed

Certain symptoms associated with coronary disease namely angina pectoris and the pain and prostration of acute coronary thrombosis are more often found in sensitive mentally overworked and frequently robust or stout professional and business men than in other individuals. Whether coronary thrombosis is actually more common in such persons has not yet been shown but one has the definite impression that it is less common in the lean laborer or farmer further study of this important point is however essential

One of the most impressive clues in our studies to date is anthropologic the majority of the young cases are not only male but mesomorphic (muscular type) there being no pure ectomorphs (very lean type) in the series although there are mixtures of mesomorphy with ectomorphy and, more often of mesomorphy with endomorphy (fat type with large abdomen) Does the muscular metabolism of the robust mesomorphic male play a role in the early development of serious coronary atherosclerosis? Especially so if he makes but little use of his muscles?

The effect of climate has not yet been adequately studied in relation to the incidence of coronary heart disease

Alcohol tobacco tea and coffee are probably without direct influence except that in occasional individuals the symptom of coronary insufficiency namely angina pectoris is precipitated or aggravated by excessive use of tobacco while heavy indulgence in alcohol over many years may have a damping influence on the symptoms but not otherwise on the ill effects of coronary heart disease

Heredity as already mentioned does appear to exert a definite action There may well be an inherited family coronary arterial tree in some families more branching and interlacing may occur than in others who are prone to develop coronary heart disease This important point needs accurate evaluation Probably however of more importance is the inheritance of body build that is of mesomorphy mentioned above and of a metabolic fault whereby atheroma is favored The hereditary predisposition to certain diseases which favor the occurrence of presenile coronary heart disease namely diabetes mellitus xanthomatosis and hypertension is certainly an important consideration Hereditary hypercholesterolemia and familial xanthomatosis in a series of 35 families (172 members) and 29 individuals with 40 per cent showing coronary heart disease constituted an inherited incomplete dominant trait (Adlersberg and Parets 1949) Familial liability to sudden coronary death was reported by Herapath and Perry in 1930 in the persons of a father aged 42 and of his three sons aged 43 31 30

**Pathology** A discussion of coronary artery atherosclerosis itself and of other coronary artery diseases has been presented under the preceding section of Etiology and need not be repeated here

The effect of coronary disease on the heart is extremely variable in degree and rapidity of involvement There may be only ischemia without structural

change there may be slight fatty degeneration generalized or local with a late sequela of slight fibrotic change there may be extensive changes due to single or multiple infarctions which are so gradual in development that the heart remains competent though with lowered reserve the fibrosis occurring in limited small or large areas or diffusely or there may be a suddenly developed myocardial infarct small or large fatal or outlived involving one part or another of the left ventricle rarely the right ventricle or both ventricles and due to occlusion by thrombosis or embolism of one of the main coronary artery branches The size of the infarct the prognosis the process of repair and the completeness of healing depend on several factors the size of the artery occluded the rapidity of occlusion the extent of either congenital or acquired anastomotic or collateral coronary circulation (and possibly also of other blood channels including the Thebesian circulation and extracardiac blood vessels in the pericardial attachments) and the effectiveness of treatment

The major and by far the most important source of the collateral coronary circulation that so often rescues the myocardium from anoxia is undoubtedly the multitude of small anastomotic arterial branches themselves which gradually grow larger and more and more competent to supply the need through the years

The Thebesian vessels are small channels opening into the heart chambers especially the ventricles of varying numbers and size they connect directly with coronary capillaries and veins and by sinuses with the arterioles and probably are the vestiges of the intertrabecular spaces of the primitive ventricle whereby blood was brought into contact with the cells of the myocardium before the development of an adequate coronary circulation These Thebesian vessels are of uncertain function and value but sometimes they and especially other blood sinuses which link up various parts of the coronary circulation may well be helpful when the regular channels of blood supply to the myocardium are obstructed as in rare reported cases in which life continues for a while in spite of complete and chronic occlusion of both coronary arteries in such cases however highly placed and anastomotic coronary arterial branches proximal to the points of block doubtless play the major role in maintaining the myocardial circulation Compensatory circulation to the myocardium by way of extracardiac vessels developing over the pericardial attachments or adhesions as from the bronchial arteries is probably sometimes available in addition to the blood supply via the Thebesian vessels and the myocardial blood sinuses but adequate blood vessels of the sort would seem to be rare this idea has however pointed to the possible value of artificially introducing blood supply from the outside and Beck and O Shaughnessy have done this in man the former using at first the pectoral muscle (1935) and the latter the omentum through the diaphragm (1937) work which still remains in the experimental stage and in which other techniques are being tried (Beck 1948)

The descending branch of the left coronary artery near its mouth is the place most commonly affected both by extensive sclerotic change and by

thrombosis When there is a sudden occlusion at this spot an infarct usually appears in the anterior wall of the left ventricle near the apex and often involves also the anterior and lower part of the interventricular septum (Figure 106A) This is the commonest site of cardiac infarction and the descending branch of the left coronary artery has as a result of its lethal role been called the artery of sudden death The preponderance of involvement of this artery and of this part of the left ventricle is not however so great as used to be



FIG 106A Photograph showing a large fibrosed cardiac infarct about four months old in the anterior and apical part of the left ventricle involving the septum and the base of the papillary muscles and resulting from thrombosis of the descending branch of the left coronary artery with mural thrombus in the cardiac aneurysm resulting from the infarct This lesion was found in a man 68 years old

believed it is only slightly in the lead The reason for the erroneous idea of some years ago was that a careful enough search was not always made for old scars at other sites and also because there was more often recovery from infarcts in other sites and patients leaving the hospitals were lost to view

The second most likely spot for infarction is the posterior wall of the left ventricle near the base behind the posterior cusp of the mitral valve due usually to occlusion of the right coronary artery or of the circumflex branch of the left (Figure 106B)

The relative frequency of thrombosis of the three larger coronary arterial trunks in a series of 49 cases of myocardial infarction found in 1 000 consecutive autopsies at the Mayo Clinic was as follows anterior descending branch

of the left in 28 cases right coronary 20 cases and circumflex branch of the left 17 cases (Barnes and Ball 1932) In that series of cases the infarct involved the apex and anterior portion of the left ventricle in 25 cases and the posterior basal portion of the left ventricle in 21 cases while the remaining 3 hearts showed two infarcts one at the apex and one at the base In another series of 34 cases (Saphir et al 1935) both coronary arteries were involved in all of the cases but the more severe lesions were found in the anterior descending branch of the left There was involvement of at least two coronary



FIG 106B Photograph showing a small fibrosed cardiac infarct (A) in the posterior wall of the left ventricle at the base just below the posterior cusp of the mitral valve (which is lifted up) Note the whitened thickened endocardium and the small patch of adherent pericardium (B) overlying the infarct. The left ventricular wall at the apex is somewhat thinner than usual but is not the site of any localized infarct From a man of 80 years of age the acute coronary thrombosis had occurred at the age of 63

branches supplying each infarcted area a fact of great significance in helping to explain various clinical electrocardiographic and pathologic anatomic discrepancies that have been noted in recent years An interesting and important observation in this study was that although in general there was agreement between the infarcted areas and disease of the particular arterial trunks directly supplying these areas occasionally a recent thrombus was found in one coronary artery while the most recent infarct was located in an area supplied by the previously occluded opposite artery obviously the area before becoming infarcted had been supplied by collateral anastomoses Further evidence of the very complicated state of affairs in coronary thrombosis has been supplied by Sprague and Orgain (1935) in an analysis of 3 889 autopsied cases

at the Massachusetts General Hospital 131 showed some degree of coronary occlusion but acute coronary thrombosis with occlusion limited to a single coronary artery or branch was found to be relatively infrequent only 17 of 61 cases of acute coronary thrombosis showing such limitation complete or recanalized thrombosis of a main artery or a main branch was discovered in the left coronary circulation in 46 cases and in the right in 21. In a recent analysis of a 20 year experience at the Massachusetts General Hospital the left coronary artery was found to be thrombosed much more commonly than the right and anterior wall infarcts were twice as common as the posterior and more serious, as evidenced by the fact that of the 23 cases of rupture 22 were through the anterior wall (Wang et al 1948).

It has remained for Blumgart and Schlesinger (1940) to clarify much more fully this hitherto confused and difficult problem of the relationship between coronary occlusion myocardial infarction and fibrosis and clinical manifestations by the study of 355 consecutive cases examined post mortem by special injection roentgenologic and dissection technic. They concluded (1) that in normal hearts intercoronary anastomoses though present are of little functional significance in obviating the untoward effects of sudden coronary narrowing or occlusion (2) that the apparent inconsistency between the presence of long standing obstructive arterial lesions and the absence of significant pathologic or clinical evidence of myocardial damage was dispelled by the demonstration of a collateral circulation (which had gradually developed) serving as a by pass in relation to the obstruction in each of these hearts (3) that in some instances of acute myocardial infarction caused by acute coronary occlusion the fresh thrombus may be found distant from the infarct in a vessel serving as a source for the collateral circulation supplying that area (for example fresh infarction of the anterior wall of the left ventricle precipitated by a fresh occlusion in the right coronary artery which was serving as a source of collateral circulation to that area in the place of the old occluded anterior descending left coronary artery) and (4) that every patient suffering primarily from angina pectoris without evidence of valvular disease or arterial hypertension will show at postmortem examination old complete occlusion of at least one major coronary artery.

Narrowing or occlusion of the smaller coronary branches may be completely compensated for by a rich collateral circulation often it is not so compensated however and small localized areas of infarction result which are without symptoms or signs unless an especially important part of the heart is involved such as the atrioventricular node (of Tawara) and bundle (of His) with the production of heart block. Infarction of the base of the interventricular septum may lead to atrioventricular or intraventricular block or even to perforation of the septum.

*Cardiac infarction* results from the blocking off of blood supply to a part of the heart. There follows necrosis of the tissue (Figure 107) chiefly of the myocardium often also of the pericardium if the infarct is large enough to extend to this structure but infrequently of the endocardium which very probably receives

much of its blood supply directly from the ventricular chamber. If the pericardium is affected a sterile fibrinous pericarditis occurs and if the endocardium is involved a thrombus is likely to form over it in the ventricular (or rarely atrial) cavity. Most intraventricular thrombi after cardiac infarction



FIG. 107 Microphotographs of myocardial infarcts secondary to coronary disease (A) Acute stage with invasion of leukocytes and beginning necrosis of muscle fibers (B) Subacute stage with almost complete disappearance of damaged muscle fibers and beginning organization of scar with several small blood vessels. A few undamaged muscle cells remain near one of the small arteries (C) Old fibrous scar involving part of the myocardium and penetrating to the endocardium (to the left) (kindness of Drs. F. H. and Kenneth Mallory, Massachusetts General and Boston City Hospitals, Boston.)



however are laid down in the more or less stagnant pockets (sometimes frank aneurysms) where the infarcted heart wall is thinned and noncontractile even though the endocardium itself is intact. Such thrombi may form over old scars as well as over fresh infarcts (Mallory White and Salcedo Salgar 1939). It is from such intraventricular mural thrombi that emboli are frequently detached to cause serious complications after acute coronary occlusion, less often in the case of old scars. It was largely to prevent such clots that anti-coagulant therapy was introduced in the treatment of acute myocardial infarction. Infarction of the atria is rare even if carefully looked for, probably because the wall is thin and in large part supplied directly from the atrial cavities.

If the patient survives the immediate shock of the coronary occlusion and the acute cardiac dilatation and failure that sometimes follow, the process of repair begins and is complete after some weeks or months (depending on the size of the infarct and the adequacy of the circulation in its neighborhood), leaving a fibrous scar of greater or lesser extent (Figure 107). In the process of repair there occurs thinning and weakening of the ventricular wall which lead not rarely to cardiac aneurysm and during the acute stage even to rupture with fatal hemorrhage into the pericardium.

Rupture of the heart when not traumatic or due to uncommon infectious processes (abscesses) is caused by recent almost never by old cardiac infarction from coronary occlusion; such a mechanism is responsible almost invariably during the first ten to fourteen days of the infarct (Jetter and White 1944; Friedman and White 1944). In a series of 270 cases of myocardial infarction among 2,967 autopsies at the Massachusetts General Hospital between March, 1933 and November 1940, cardiac rupture was found in 10 (3.7 per cent) all among the 105 cases of fresh infarction (9.5 per cent) and none among the cases with old infarcts; and the same percentage (9.5) was reported by Diaz Rivera and Miller in 1948, all in acute cases too. This was in contrast to rupture of the heart in 16 (73 per cent) of 22 cases of acute myocardial infarction among psychotic patients in whom both diagnosis and treatment were difficult. Rupture involves the ventricular septum in some cases, actually 20 per cent of 76 among 28,657 autopsies reported by Furnam and Meneely (1948); it should be diagnosed correctly ante mortem although only five such were found among 36 collected in the literature by Rabinovich (1947). The papillary muscle may also rupture.

Sometimes lime salts or even bone are laid down in the old necrotic area of the infarct, as may also happen in a more gradual way in other parts of the heart from faulty circulation or disturbed metabolism, producing masses of calcification in papillary muscles or stony rings at the bases of mitral and aortic valves.

When there is marked narrowing of the coronary arteries, with or without actual occlusion here or there, angina pectoris and sudden death are quite common; the myocardium itself may or may not show fibrosis or areas of infarction in such cases, but it is always ischemic. In their classic studies Blumgart

and Schlesinger (1937 1940) have presented evidence that temporary ischemia may cause irreversible myocardial changes and that if the ischemia is of sufficient duration even without acute vascular occlusion myocardial infarction may result of the same character and degree as that which occurs after permanent and complete coronary occlusion

The heart may or may not be enlarged as the result of coronary disease with simple sclerosis and little or no strain on the damaged heart there is no change or possibly even a slight decrease in size but with healing after a large infarction especially if there is much strain well marked enlargement may result Horne and Weiss (1935) who followed with roentgen ray study 20 patients who had a normal sized heart at the time of coronary thrombosis found no evidence of enlargement over a period of nine months to nine years and ten months but Bartels and Smith (1932) on the other hand in an autopsy study of the hearts of 42 cases of myocardial infarction in which all other known or supposed causes of cardiac hypertrophy (such as hypertension) were excluded found definite gross cardiac hypertrophy in 37 (88 per cent) the average increase in weight above the estimated normal being 132 gm My own experience is nearer that of Bartels and Smith but it is the size of the infarct and the presence or absence of complications that determine whether or not the heart will be enlarged when there is but a small infarct or angina pectoris alone without complications the size of the heart may remain within normal limits

Cardiac aneurysms ruptures of the heart cardiac infarcts old and new and fatty and fibrotic changes of lesser extent have been known to pathologists for centuries and their connection with coronary disease recognized post mortem for many years but in the practice of medicine these conditions have been regarded as of much clinical significance and possible to diagnose readily only during the present generation

**Symptoms** The production of symptoms in heart disease of coronary origin is dependent on several factors in particular the sufficiency of the coronary circulation with relation to the degree of activity to which the myocardium is subjected and also the speed of development of myocardial change the extent of the damage the adequacy of coronary arterial anastomoses the amount of strain on the damaged heart and the sensitiveness of the nervous system of the victim If coronary narrowing and obstruction and even cardiac infarction develop slowly and there is no excessive cardiac strain there may be no symptoms at all though there be extensive areas of damaged muscle and though one or both coronary arteries be occluded The reserve strength of both myocardium and its blood supply is normally very great and not easily exhausted

If however sudden occlusion of a large coronary artery occurs with inadequate collateral coronary circulation the symptoms may be extreme with terrible pain shock and sometimes death Between these two extremes of symptoms in coronary heart disease from none at all to those that are overwhelming there may be found all grades and varieties Sometimes the symp-

toms much exaggerated by nervousness or neurocirculatory asthenia in a particularly sensitive individual are out of all proportion to the amount of heart damage and disability

The two most common symptoms of coronary heart disease are pain and dyspnea. It is difficult to obtain accurate figures for the relative frequency of these two symptoms since some old persons though limited by slight substernal oppression or dyspnea on exertion do not make much of these limitations which they ascribe to old age, they may even find it difficult to distinguish between substernal oppression and dyspnea. On the whole oppression is the more common symptom and is due to the inability of the damaged coronary arteries to maintain an adequate circulation in the heart muscle. Other symptoms also occur particularly palpitation, but they are less characteristic.

*Pain in coronary heart disease is of different sorts and degrees.* It may consist of slight moderate or severe, high, mid or low substernal oppression transient on exertion that is angina pectoris there may be extreme substernal and epigastric oppression lasting for hours and sometimes followed by collapse due to coronary thrombosis or there may be slight to moderate precordial aching due commonly to an associated neurocirculatory asthenia. The precordial aching is more commonly found in other conditions than in coronary heart disease the angina pectoris is infrequently found in other conditions and the pain of coronary thrombosis is never like that found in other conditions except when it is atypical and so low in position that it simulates pain of gastrointestinal or gallbladder origin or in very rare cases may be mistaken for the pain of a dissecting aortic aneurysm or for that due to pulmonary embolism. The transient oppression due to coronary insufficiency that is angina pectoris may almost exactly be simulated in position and character and duration by the discomfort due to spasm of esophagus or upper end of the stomach (cardiospasm) or indeed one symptom may excite the other the differentiation is generally quite clear in the positive relationship of angina pectoris to effort.

The name angina pectoris (Latin *angina* from the Greek *α/χνη* strangling and *pectus* breast bone or breast) was introduced by Heberden in 1768 to describe this characteristic symptom which has been also called stenocardia.

Heberden William. Some Account of a Disorder of the Breast. *Medical Transactions Royal College of Physicians London 1772* Volume 2 page 59. The original mention of angina pectoris was made by Heberden at a lecture before the Royal College of Physicians of London in July 1768 but not published until 1772.

The entire lecture is herewith presented as published in 1772.

There is a disorder of the breast marked with strong and peculiar symptoms considerable for the kind of danger belonging to it and not extremely rare of which I do not recollect any mention among medical authors. The seat of it and sense of strangling and anxiety with which it is attended may make it not impropely be called Angina pectoris.

"Those who are afflicted with it are seized while they are walking and more particularly when they walk soon after eating with a painful and most disagreeable sensation in the breast which seems as if it would take their life away if it were to increase or to continue the moment they stand still all this uneasiness vanishes. In all other respects the patients are at the beginning of this disorder perfectly well and in particular have no shortness of breath from which it is totally different.

"After it has continued some months it will not cease so instantaneously upon standing still and it will come on not only when the persons are walking but when they are lying down and oblige them to rise up out of their beds every night for many months together and in one or two very inveterate cases it has been brought on by the motion of a horse or a carriage and even by swallowing coughing going to stool or speaking or by any disturbance of mind. I have heard once and only one person say that he had known it attack him while he was up and standing still or sitting. But most whom I have seen have been perfectly unaffected with riding in any manner with speaking swallowing laughing sneezing or vomiting. One has told me that this complaint was greatest in winter another that it was aggravated by warm weather in the rest the seasons were not suspected of making any difference.

I have observed something like this affection of the breast in one woman who was paralytic and have heard one or two young men complain of it in a slight degree but all the rest whom I have seen who are at least twenty were men and almost all above 50 years old and most of them with a short neck, and inclining to be fat.

When a fit of this sort comes on by walking its duration is very short, as it goes off almost immediately upon stopping. If it come on in the night, it will last an hour or two and I have met with one in whom it once continued for several days during all which time the patient seemed to be in imminent danger of death.

When I first took notice of this distemper and could find no satisfaction from books I consulted an able physician of long experience who told me that he had known several ill of it and that all of them had died suddenly. This observation I have reason to think is generally true of such patients having known six of those for whom I have been consulted die in this manner and more perhaps may have experienced the same death which I had no opportunity of knowing. But though the natural tendency of this illness be to kill the patients suddenly yet unless it have a power of preserving a person from all other ails it will easily be believed that some of those who are afflicted with it, may die in a different manner since this disorder will last as I have known it more than once near twenty years and most usually attacks only those who are above fifty years of age. I have accordingly observed one who sunk under a lingering illness of a different nature.

The os sterni is usually pointed to as the seat of this malady but it seems sometimes as if it was under the lower part of it, and at other times under the middle or upper part but always inclining more to the left side and sometimes there is joined with it a pain about the middle of the left arm. What the particular mischief is which is referred to these different parts of the sternum it is not easy to guess and I have had no opportunity of knowing with certainty. It may be a strong cramp or an ulcer or possibly both.

"The opinion of its being a convulsion of the part affected will readily present itself to any one who considers the sudden manner of its coming on and going off the long intervals of perfect ease the relief afforded by wine and spirituous

cordials the influence which passionate affections of the mind have over it the ease which comes from varying the posture of the head and shoulders by straightening the vertebrae of the thorax or by bending them a little backwards or forwards the number of years which it will continue without otherwise disordering the health its generally bearing so well the motion of a horse or carriage which circumstance often distinguishes spasmodic pains from those which arise from ulcers and lastly its coming on in certain patients at night just after the first sleep at which time the incubus convulsive asthmas numbness epileptics hypochondriac languors and other ills justly attributed to the disturbed functions of the nerves are peculiarly apt either to return or to be aggravated

"The pulse is at least sometimes not disturbed by this pain and consequently the heart is not affected by it which I have had an opportunity of knowing by feeling the pulse during the paroxysms but I have never had it in my power to see any one opened who had died of it the sudden death of the patients adding so much to the common difficulties of making such an enquiry that most of those with whose cases I had been acquainted were buried before I had heard that they were dead

But thought it be most probable that a strong spasm be the true cause of this disorder yet there is some reason for thinking that it is sometimes accompanied with an ulcer and may partly proceed from it for I have seen two of these patients who often used to spit up blood and purulent matter one of whom constantly asserted that he felt it come from the seat of the disorder Another had a painful sensation in swallowing and upon pressing the part which seemed to be affected From a fourth who fell down dead without any notice there immediately arose such an offensive smell as made all who happened to be present judge that some foul abscess had just then broken

Bleeding vomits and other evacuations have not appeared to me to do any good Wine and cordials taken at going to bed will prevent or weaken the night fits but nothing does this so effectively as opiates Ten fifteen or twenty drops of Tinctura Thebaica taken at lying down will enable those to keep their beds till morning who had been forced to rise and sit up two or three hours every night for many months Such a quantity or a greater might safely be continued as long as it is required and this relief afforded by opium may be added to the arguments which prove these fits to be of a convulsive kind Time and attention will undoubtedly discover more helps against this teazing and dangerous ailment but it is not to be expected that much can have been done towards establishing the method of cure for a distemper hitherto so unnoticed that it has not yet as far as I know found a place or a name in the history of diseases

Later Heberden added more cases of angina pectoris to his twenty-odd men mentioned in the original lecture quoted above and in 1786 in a chapter entitled *Pectoris Dolor* in his *Commentaries on the History and Cure of Diseases* (which was translated and published by his son William Heberden Jr in 1802 a year after his own death) he wrote as follows I have seen nearly a hundred people with this disorder out of which number there have been three women

Although coronary thrombosis is more likely than not to be attended by severe exhausting crushing substernal pain often radiating to either arm or both arms neck head or back as in angina pectoris there are exceptions without any pain at all in such cases there may be dyspnea instead or simply

collapse or prostration. In some groups of cases of coronary thrombosis the incidence of pain may be surprisingly low as in one series of 76 patients with coronary thrombosis proved at postmortem examination in which only 36 (47 per cent) gave a history of pain 29 (38 per cent) gave a history of no pain and the remaining 11 died suddenly (Davis 1932) in another group of 100 cases reported by Gorham and Martin (1938) cardiac pain was noted in 58 per cent. In my own experience however pain is more common than indicated by these figures a review of 56 consecutive unselected cases of my own proved at autopsy has revealed the occurrence of pain in all but two (96.4 per cent) severe in 34 (61 per cent) moderate in 10 (18 per cent) and mild in 10 (18 per cent) (with the help of Dr F. W. Miskall). The pain may be quickly masked by collapse or a moribund state or concealed by other symptoms or even by medication or alcoholism or indeed on occasion not adequately sought for.

The similarity of the character and the position of the pain of coronary occlusion to that of paroxysmal angina pectoris is a strong argument that coronary disease by limiting the blood supply to the heart muscle is the commonest cause of angina pectoris.

Dyspnea may vary from a slight breathlessness on exertion to the awful struggling respiration of marked cardiac asthma dependent on the severity and suddenness of failure of the involved left ventricle which causes vascular engorgement of the lungs. Finally instead of pain as classically described a sudden onset of dyspnea with or without pulmonary edema or of Cheyne Stokes respiration may also occur as an accompaniment of left ventricular weakness due to acute coronary occlusion or to chronic coronary heart disease particularly in individuals with very limited myocardial reserve to start with. Moreover angina pectoris sometimes initiates such dyspneic attacks. Sighing respiration noted in occasional cases is due to the nervous state of the patient and not to his heart disease.

*Palpitation* is frequently complained of by patients with coronary heart disease chiefly because of the occurrence of arrhythmia. Such arrhythmia is usually of relatively little importance consisting as it does for the most part of premature contractions chiefly of ventricular origin. However two additional observations should be made regarding premature beats and coronary heart disease in the presence of coronary insufficiency premature beats may on occasion be painful due doubtless to the short diastolic rest and secondly premature beats induced by exercise suggest the possibility of an underlying deficiency of the coronary circulation. Occasionally paroxysmal auricular tachycardia and atrial fibrillation are also found as complications of coronary heart disease they are somewhat more important than premature beats. Finally paroxysmal ventricular tachycardia and atrioventricular block either partial or complete are the most serious disorders of mechanism which may occasion palpitation the former is particularly of ill omen but fortunately very rare. These two disturbances of the heart beat will be discussed in Chapters 32 and 34 respectively.

*Prostration or collapse*, sometimes of high degree is a frequent early symptom of acute coronary occlusion due to a state of vasomotor shock or peripheral vascular failure which may in itself be fatal in a few cases prostration like dyspnea may replace pain as the chief symptom of acute myocardial infarction especially in very old persons Syncope as a much less important nervous reaction may be a rare complication even in angina pectoris and as such was once unnecessarily and confusingly designated syncope anginosa (Parry 1799)

Other symptoms occurring with coronary heart disease are either infrequent unimportant or due to complications General weakness is occasionally seen in older persons who have arteriosclerosis elsewhere The same is true of mental disturbances faintness dizziness and even coma and convulsions except that cerebral anemia due to high grade heart block resulting from coronary disease may give rise to the *Adams Stokes syndrome* (faintness syncope and convulsions with a slow pulse) Prolonged coma lasting for hours or days especially in aged persons may follow rarely the temporary or prolonged drop in blood pressure that sometimes accompanies acute coronary thrombosis Congestive failure may result in cough hemoptysis gastrointestinal symptoms ascites and edema Sweating restlessness and vomiting are common symptoms at the onset of coronary thrombosis the vomiting however is more often induced by the opiate used in treatment than by the heart attack per se Hiccough is rare

Coronary thrombosis leading to myocardial infarction usually causes fever for a few days with a temperature rising to 101° or 102° F rectally the grade and duration depending on the size of the infarct undergoing necrosis (Figure 108) Also the cardiac lesion may give rise acutely to various local pains due to visceral cerebral or peripheral embolism resulting from the discharge into the circulation of pieces of the mural thrombus in the left ventricle pulmonary embolism may occur from thrombosis in the veins of legs or pelvis or from thrombi in the right ventricle whether due to right ventricular (usually septal) infarction or to stasis

**Signs** There are frequently no signs of coronary heart disease and the patient may give the appearance of perfect health This is especially true in the case of uncomplicated angina pectoris on effort When there is however a high degree of coronary insufficiency there is often a rather characteristic sallow unhealthy tint to the skin suggesting on occasion slight jaundice or anemia The patient is sometimes an obviously sick man at first glance and this is particularly true during the state of shock that may occur at the time of an acute extensive coronary thrombosis

A considerable amount of coronary disease may exist with little or no cardiac enlargement but a very large myocardial infarct or congestive failure whether limited to the left ventricle or involving the entire heart is always attended by cardiac enlargement easily found both by physical examination and by roentgen ray The enlargement may come rapidly with cardiac infarction it then consists chiefly of dilatation of the left ventricle but it may involve

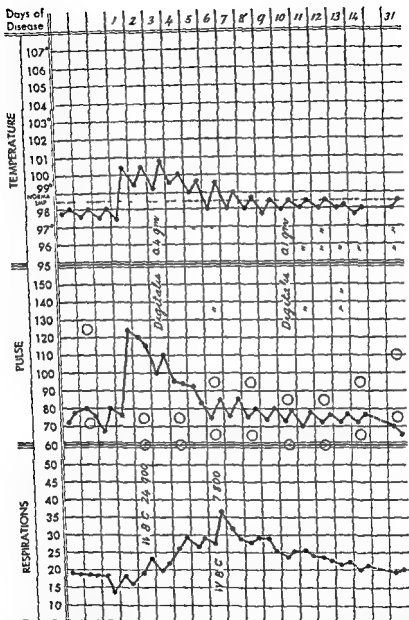


FIG 108. Chart in acute coronary thrombosis causing a large cardiac infarct showing temperature (mouth) pulse rate respiratory rate and blood pressure. The patient male, 52 years old was in bed under observation and treatment for angina pectoris decubitus when the myocardial infarction occurred. He recovered but died suddenly a year later. Digitalization was carried out with beneficial results upon the onset of dyspnea due to dilatation and failure of the left ventricle. The blood pressure is designated by circles open for systolic pressure and dotted for diastolic. The leukocytosis at onset was unusually high but quickly subsided.



also the right ventricle when the left ventricle fails as the process of repair goes on hypertrophy develops being apparently a compensatory measure. From coronary heart disease (thrombosis with infarction) alone the heart may increase in weight to 500 or 600 gm (normal weight about 300 gm).

The heart sounds are frequently weakened in coronary heart disease especially the first sound at the apex shortly after coronary thrombosis sets in sometimes a so-called tic tac rhythm results from this weakening of the first sound. Gallop rhythm protodiastolic in time is especially common with left ventricular dilatation and weakness following coronary thrombosis. Reduplications and gallop rhythm may also occur with the development of intraventricular and atrioventricular block. The pulmonary second sound becomes accentuated if the left ventricle fails. Murmurs may or may not occur the commonest is that of functional mitral regurgitation due to dilatation—an apical systolic murmur. Basal murmurs are less common in coronary heart disease an aortic systolic murmur may be found due to aortic dilatation resulting from an associated hypertension. Sometimes such a murmur is due to slight aortic stenosis caused by sclerotic involvement of the aortic valve, if aortic stenosis is marked with systolic thrill felt over the aortic area it is rarely to be ascribed to a simple atherosclerotic change in the aortic valve but more often to the result of an old infectious process with superimposed calcification. An aortic diastolic murmur is not found in coronary heart disease unless there is a complication of syphilitic aortitis, aortic stenosis with regurgitation, chronic hypertension with dilated aortic valve ring or rarely senile ectasia of the aorta (see Chapter 28).

A pericardial friction rub frequently accompanies cardiac infarction especially if the infarct is large it appears usually on the second or third day of illness and is transient disappearing in a day or two—rarely it lasts for a week or more.

The arrhythmias found in coronary heart disease have already been mentioned (see page 541) the most common being premature beats and atrial fibrillation the atrial fibrillation is either paroxysmal (about 33 per cent) or permanent (67 per cent) in type.

The pulse rate varies widely in coronary heart disease from a normal range in most cases to a tachycardia of 120 or more in some cases with vasomotor shock or congestive failure in acute coronary thrombosis or with abnormal rhythm rarely there is a bradycardia which may be marked (down to 30) if high grade heart block supervenes.

The blood pressure in uncomplicated coronary heart disease is normal or low. Severe cardiac infarction following coronary thrombosis is however characteristically attended by a sharp fall in systolic blood pressure whether or not it has previously been high (because of hyperpiesia). The low blood pressure of 75 to 100 mm mercury systolic and 50 to 75 diastolic may continue for days, tending gradually to resume the level that existed before the coronary thrombosis or a somewhat lower level it is the combined result probably of vasodilatation, myocardial weakness, sedative drugs and rest. In

a few cases the blood pressure is elevated by the pain during the acute episode of infarction. I have encountered cases whose blood pressure was normal before and after the acute coronary occlusion but considerably increased at the time of the attack. In a good many other patients with small- and medium-sized infarcts the blood pressure is unaffected except for slight reduction with bed rest. During periods of higher degrees of coronary insufficiency (sometimes lasting for weeks) the diastolic pressure may be slightly elevated (to 95, 100 or 105 mm).

Roentgenologic study may show no abnormality whatsoever though the aorta is often distinctly tortuous and elongated from atheroma with prominence of the knob and sometimes with visible calcification. Roentgen ray examination usually shows cardiac enlargement after myocardial infarction and sometimes a bulge at or just above the apex due to a cardiac aneurysm (Figure 125 page 657). In the case of extreme cardiac infarction the action of the heart may be obviously weak and the pulmonary artery and lung hilus shadows may be prominent due to pulmonary vascular engorgement secondary to failure of the left ventricle. Fluoroscopy and kymography often reveal the site of the infarct as comprising a section of the left border of the heart shadow which shows little or no systolic pulsation or indeed even a paradoxical out-thrust instead of retraction in systole. In such cases as a rule however the diagnosis is obvious by other methods of examination.

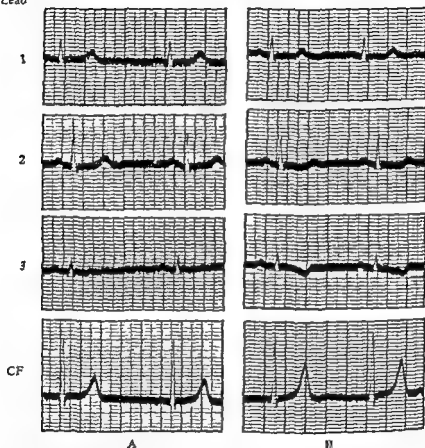
Calcified coronary arteries can sometimes be made out on the roentgenogram but this finding is of little or no clinical value since serious coronary heart disease may occur without it and since coronary calcification can be present without coronary insufficiency due to an adequate collateral circulation. Roentgen visualization of the coronary arteries is possible by retrograde aortic or arterial injection of contrast (Diodrast) fluid or by direct left ventricular puncture (see Chapter 7) but it would seem to be unwise to subject cases suspected of having coronary heart disease to a possible hazard in this procedure.

*Electrocardiograms are of the greatest importance.* They are often normal with slighter degrees of coronary heart disease especially between (not during) attacks of angina pectoris but in advanced coronary heart disease they usually show changes in the Q and T waves and often in the ST segments. less frequently they show the presence of intraventricular block and low voltage. uncommonly there is atrioventricular block. The commonest cause of heart block is coronary disease. Other disturbances of the heart beat are readily shown by electrocardiography. Left ventricular preponderance is not commonly found unless there is an associated hypertension; it may however follow myocardial infarction with left ventricular hypertrophy and dilatation.

There are a few relatively simple comments to make about the fundamental principles of electrocardiography in coronary heart disease before discussing detailed patterns. In the first place there may be areas small or large of myocardium affected by the faulty blood supply; sometimes the area is so microscopic that it may not show at all unless nodal or a v conduction tissue

involved or such a large area or multiple areas are affected that the picture is very complicated one lesion neutralizing or confusing somewhat the effects of another. It is surprising that so often the patterns are so clear-cut indicating isolated or preponderant lesions. In the *second* place an effect on the electrocardiogram may be transient due to ischemia as during angina pectoris (Figure 109) or a combined effect of ischemia and of a destruction of muscle old or new also. In the *third* place it is often possible to focus accurately over the

Lead



A

B

FIG 109 - Electrocardiograms taken during an attack of angina pectoris (B) and while free from pain (A) male age 52. Note depressed ST segments in Lead 2 sharp inversion of T waves in Lead 3 and unusually high T waves in Lead CF of the record during angina pectoris. Time = 0.04 and 0.20 second amplitude 1 mm = 0.10 mv

area involved by unipolar leads around the chest wall or in the esophagus or in the heart itself (by catheterization) which illustrates the value of multiple chest leads in fact even more on occasion than the six that have been routinely adopted. And here I would urge the use of the V leads of Wilson rather than those using one extremity as the indifferent lead point (see Chapter 9). In the *fourth* place it is important to remember that a myocardial lesion

■ a dead or blind spot or window and so reflects the action current elsewhere especially through the heart in the focus of the lead this accounts for the presence of a *Q* wave and the loss of an *R* wave (intrinsic deflection) over a myocardial scar In the *fifth* place the left ventricle is where most of the effects of coronary obstruction are to be found most commonly in the anterior wall but quite often in the posterior wall and septum too and even in the lateral wall although that is more often involved with either an anterior or posterior wall lesion the right ventricle and the atria are per se uncommonly involved quite possibly because of their thinner walls which are more readily supplied by the intracardiac blood stream or by ■ richer coronary network or both Finally the electrocardiogram may change slowly or unexpectedly in coronary heart disease and therefore isolated records are often valueless serial records are not only desirable but often essential even daily for weeks

With these introductory remarks one may mention some of the coronary patterns but for details and many illustrations the reader is perforce referred to textbooks on electrocardiography or on coronary heart disease per se The earliest effect of coronary insufficiency on the electrocardiogram whether due to temporary ischemia or muscle destruction is an alteration of the baseline of the *ST* segment (current of injury) (Smith 1918 Pardee 1920) This consists of an elevation of one or more millimeters (0.1 millivolt) immediately over the muscle affected and a depression over the opposite part of the heart

Thus precordial Leads  $V_4$  and  $V$  located over an anterior wall infarct will show an elevated *ST* segment during its early stage (Figure 110 page 548) and an esophageal lead (over the posterior wall) a depressed *ST* segment In the case of a posterior wall infarct Lead  $V_4$  or  $V_5$  will show a depressed *ST* segment in the earliest stages (Figure 111 page 549)

Meanwhile the bipolar classical limb leads reflect these various changes reciprocally in Leads 1 and 3 (Figures 112 and 113) altered by a variable position of the heart a fresh anterior wall infarct is likely to raise the *ST* segment in Lead 1 and depress it in Lead 3 while a fresh posterior wall infarct may lower the *ST* segment in Lead 1 and raise it in Lead 3 These characteristic patterns quickly evolve within a few days with a return of the *ST* segments to the baseline and an inversion of the *T* waves in Leads  $V_4$ ,  $V$  and I in the case of an anterior infarct (Figure 110) and upright (normal) *T* waves in Leads  $V_4$ ,  $V$  and I but inversion (or increased inversion) of the *T* waves in Lead 3 (and often in Lead 2) (and in the esophageal lead) in the case of a posterior infarct (Figure 111) Finally with a large anterior myocardial infarct the *R* (intrinsic deflection) disappears and is replaced by a *Q* in Leads  $V_3$ ,  $V_4$  and  $V$  ■ *Q* wave appears in Lead I along with persistence of inversion of the *T* wave for awhile or permanently (Figure 114) while with a large posterior myocardial infarct a *Q* appears or deepens in Lead 3 and at times in Lead 2 with persistence of inversion of the *T* waves in those leads for awhile and sometimes permanently (Figure 111 B) an esophageal lead in the case of a posterior infarct would show a *Q* wave and inverted *T* wave while the anterior precordial Leads  $V_4$  to  $V_6$  inclusive tend to be normal The

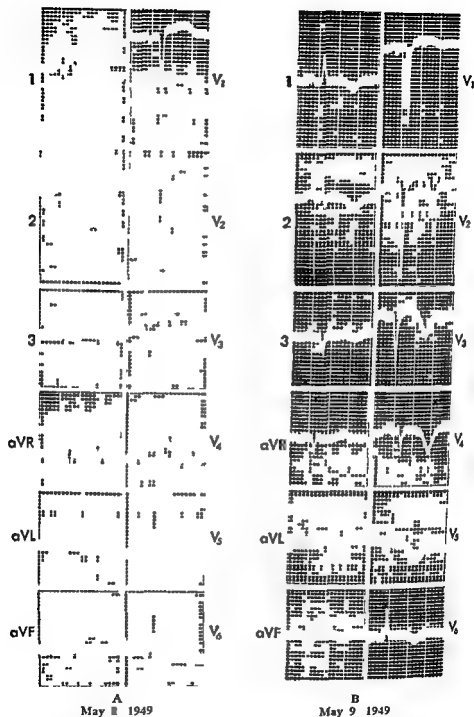


FIG 110 Electrocardiogram in anterior myocardial infarction acute stage and later Female age 45 Note especially the absence of *R* waves in Leads *V* to *V* inclusive in both *A* and *B* the elevated *ST* segment in Leads III, *V*<sub>4</sub>, *V*<sub>5</sub> and *V*<sub>6</sub> of *A* and the late inversion of *T* waves in Leads I, 2 and *V* to *V* inclusive of *B* Time = 0.04 and 0.10 second amplitude 1 mm = 0.10 mv

*Q* wave appearance (which is not constant) and the *T* wave inversion gave rise originally to the expressions  $Q_1T_1$  and  $Q_3T_3$  types of infarction (Parkinson and Bedford 1928) even before the exact sites of the infarction were identified. The *T* waves may or may not revert to normal in time but the *Q* waves remain as permanent evidence of the scars.

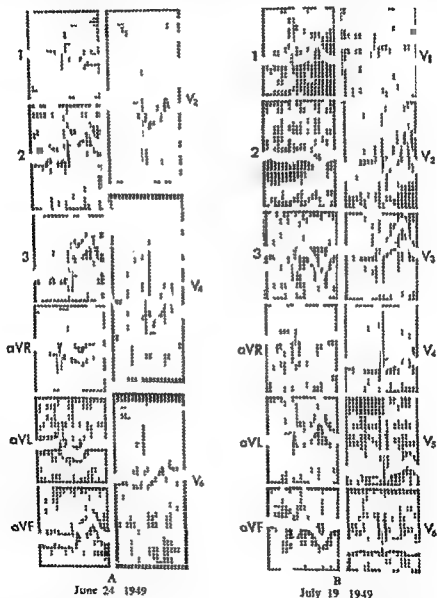


FIG 111 Electrocardiogram in acute posterior myocardial infarction male age 71. Note especially the greatly elevated ST segments in Leads 2, 3, and aVF and the depressed ST segments in Leads 1 and aVL in A and the Q waves and inverted T waves in Leads 2, 3, and aVF in B. Time = 0.04 and 0.20 second; amplitude 1 mm = 10 mv.

The commonest patterns of myocardial ischemia and infarction have been presented but there are two other sites which may occasionally be identified by electrocardiogram and still rarer ones (e.g. in atria or right ventricle) that require more exploration. A lateral wall infarct may show itself but little if it

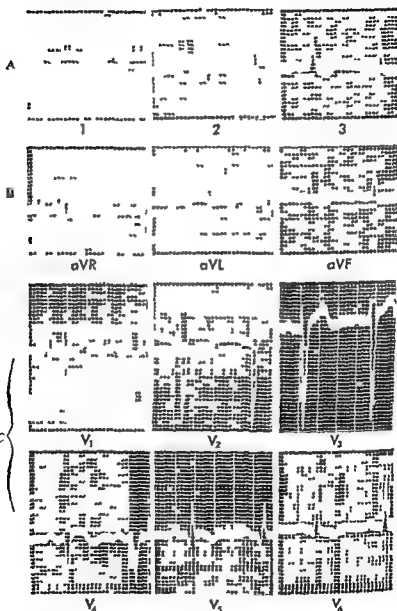


FIG 112. Electrocardiogram in a case of anterior myocardial infarction showing reciprocal ST changes in Leads 1 and 3 and Q waves and inverted T waves in Lead V<sub>1</sub>. Male age 54 (A) Bipolar limb leads 1, 2, and 3 (B) unipolar limb leads aVR, aVL, and aVF (C) six precordial leads V<sub>1</sub> to V<sub>6</sub> inclusive. Time = 0.04 and 0.20 second amplitude 1 mm = 0.10 mv

■ small Lead  $V_6$  or  $V_7$  may then reveal it by change in  $ST$  segments and  $T$  waves. As a part of a larger infarct anterior or posterior it is easily identified (Figure 115). A septal infarct is also commonly associated with anterior or

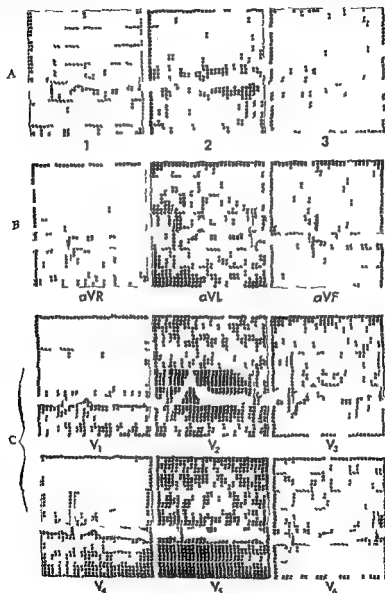


FIG. 115 Electrocardiogram in a case of posterior myocardial infarction occurring 48 hours previously and showing reciprocal  $ST$  changes. Note also  $Q$  waves and inverted  $T$  waves in Leads 2, 3,  $aVF$  and  $V_4$ . Male age 50. (A) Bipolar limb leads 1, 2 and 3 (B) unipolar limb leads  $aVR$ ,  $aVL$ , and  $aVF$  (C) six precordial leads  $V_1$  to  $V_6$  inclusive. Time = 0.04 and 20 second; amplitude 1 mm = 0.10 mv.



posterior wall infarction but shows itself by changes in the precordial leads to the right of usual left ventricular lead points that is in  $V_4$  and  $V_5$  where changes in  $ST$  segments  $T$  waves and  $Q$  and  $R$  deflections are found similar to those described for other infarct sites (Figure 116 page 554)

The unipolar limb lead records are less important as a rule than the precordial or bipolar limb curves in the case of coronary heart disease. They show

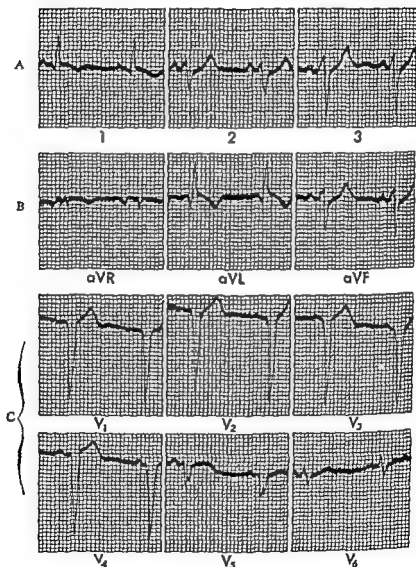


FIG 114 Electrocardiogram in a case of chronic anterior myocardial infarct male age 65 (A) Bipolar limb leads 1 2 and 3 (B) unipolar limb leads aVR aVL, and aVF (C) six precordial leads V<sub>1</sub> to V<sub>6</sub> inclusive. Note especially Q waves and inverted T waves in Leads 1 and aVL and absence of R waves in Leads V<sub>1</sub> to V<sub>3</sub> inclusive. Time = 0.04 and 0.20 second amplitude 1 mm = 0.10 mv

patterns which vary with the heart position and so give information about both position and myocardial state. For example an anterior infarct in the case of a horizontal heart will give upright *QRS* and *T* waves in Lead *VR* and inverted *QRS* and *T* waves in Lead *VL* while an anterior infarct in the case of a vertical heart will give upright *QRS* and *T* waves in Lead *VF* the limb (left arm or left leg) facing the infarct showing the most abnormality. For other discussion of precordial leads the reader is referred to Chapter 9

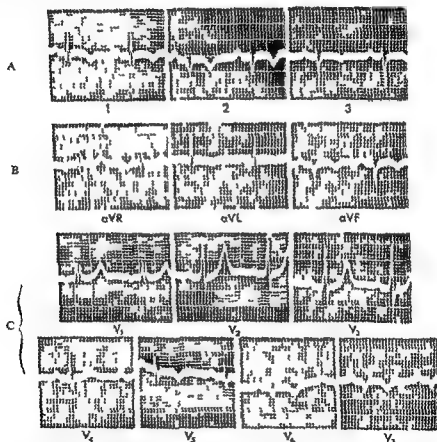


FIG 115 Electrocardiogram in a case of lateral infarct occurring one month previously male age 57 (A) Bipolar limb leads 1 2 and 3 (B) unipolar limb leads *aVR*, *aVL*, and *aVF* (C) seven precordial leads *V*<sub>1</sub> to *V*<sub>7</sub> inclusive. Note especially *Q* waves in Leads 1 2 *V*<sub>1</sub> and *V*<sub>2</sub> absence of *R* waves in Leads 2 *V*<sub>4</sub> and *V*<sub>5</sub> and inverted *T* waves in Leads 1 2 3 *aVL* *aVF* and *V*<sub>1</sub> to *V*<sub>5</sub> inclusive. Time = 0.04 and 0.20 second amplitude 1 mm = 0.10 mv

Other methods of examination reveal little of importance as a rule though the grade and duration of leukocytosis resulting from sudden cardiac infarction is a useful clue to the size of the infarct and hence to the prognosis. Usually a polymorphonuclear leukocytosis of 12 000 to 15 000 is found for three or

four days beginning a few hours after the onset of illness with an extensive infarct the white blood cell count may rise to 20 000 or more and remain elevated for a week or two The sedimentation rate of the red blood cells is accelerated in acute myocardial infarction and remains rapid for weeks until the healing process is well established

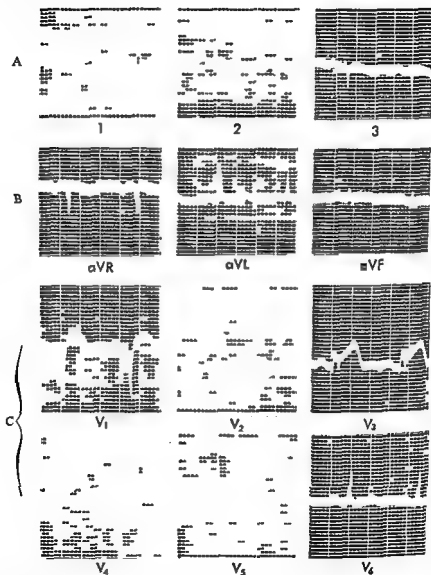


FIG 116 Electrocardiogram in a case of septal infarct female age 55 It is of interest that the limb leads show relatively little change while leads V and V are very abnormal with absence of R waves in V and elevated ST segments in V and V (A) Bipolar limb leads 1 2 and 3 (B) unipolar limb leads aVR aVL and aVF (C) six precordial leads V to V inclusive Time = 0.04 and 0.20 second amplitude 1 mm = 0.10 mv

**Course and prognosis** The course and prognosis of coronary heart disease are so variable that they must be considered individually in every case. The condition unsuspected in life may be discovered only on postmortem examination after a noncardiac death in ripe old age or symptoms and signs may be marked and obvious in a fulminating acute catastrophe of severe coronary occlusion cutting off the blood supply to a large mass of heart muscle that may kill in a few hours or a few days. The prognosis depends not only on the degree and speed of involvement of the myocardium but also on the treatment, the reserve strength of the heart and complications.

When myocardial infarction sufficiently serious to be clinically recognized occurs, the prognosis must always be guarded; most cases, however, survive the immediate attack and half of the total survive for years, a good many even for ten years or more. The first week is much the most hazardous, but danger of sudden death still exists during the second week even though all seems to be going well after the first fortnight of acute myocardial infarction recovery is the rule. Of the series of 200 cases followed by Bland and White (1941) up to the time of death or with survival for over 10 years, 38 (19 per cent) succumbed during the first month, while 50 (25 per cent) have lived more than 10 years, a much better record than was thought possible a decade ago. The longest lived proved case recorded to date survived nearly 40 years after his first attack of myocardial infarction at the age of 40 and kept at work till he was 77 (Drake, 1940), bettering the previous records of 17½ and 24½ years reported by myself in 1933 and 1937, records which had brought courage to many victims of this common condition. Just recently (1949) I re-examined a man whom I had seen at home 22 years earlier during a severe attack of acute myocardial infarction at the characteristic age of 52 years. Despite slight cardiac enlargement and an abnormal electrocardiogram he has been in excellent health for many years and plays 18 holes of golf without symptoms several times a week at 74 years of age; he continues well in 1951. Undoubtedly long survivals are frequent though recognized only relatively recently.

The prognosis is made worse in coronary thrombosis by the following findings: advanced age, a state of shock, an abrupt and prolonged marked fall in blood pressure, duration of severe substernal pain for more than twenty-four hours, fever for a week or more, especially when high at the onset (103° to 104° F), a high leukocytosis, especially if maintained for more than a week, rapid and marked cardiac dilatation, gallop rhythm, ventricular paroxysmal tachycardia, heart block, pulsus alternans, pulmonary edema with or without cardiac asthma, dropsy and embolic phenomena. It has been noted that the symptom of angina pectoris tends to disappear when congestive failure or atrial fibrillation sets in or after coronary thrombosis, although angina pectoris may recur later. It seems likely that this subsidence of angina pectoris is due, in the case of congestive failure, chiefly to restriction of activity of the patient, and in the case of myocardial infarction to the death of the muscle involved.

Paroxysmal coronary insufficiency as evidenced by the symptom of angina

pectoris on effort or even at rest (decubitus) has also like myocardial infarction a better prognosis than once was conceded. Many cases were in the past ruled out of consideration because they recovered for it was not realized that there could be such an evolution. More careful analysis and longer follow up of larger numbers of cases have doubled our expectation of the duration of life from an average of 4 to 5 years after the first symptom to one of 9 in 10 years (White, Bland and Miskall, 1943). The explanation for such longevity and frequent recovery lies in the development of a more adequate collateral coronary circulation — fortunate provision of nature. A recent follow up report of 3 440 cases of angina pectoris listed 405 who had survived ten years or more (Montgomery, et al., 1947).

**Complications** In addition to such complications as myocardial infarction, cardiac aneurysm, cardiac rupture, congestive failure, heart block and other arrhythmias and embolism from intracardiac mural thrombosis, coronary heart disease is frequently accompanied by hyperpiesia and general arteriosclerosis, sometimes by chronic rheumatic valvular disease, diabetes, nephritis and cerebral hemorrhage or thrombosis and less often by syphilitic aortitis, thyroid disease (either thyrotoxicosis or hypothyroidism), bacterial endocarditis and congenital defects. It should be added that although general or peripheral arteriosclerosis and coronary disease are often associated, they frequently occur independently of each other. One of the commonest of complications is indigestion, chiefly cardiospasm with gaseous distention of stomach or bowels, but sometimes gallbladder disease with or without stones. In frequently there is peptic ulcer. The cardiospasm is largely reflex and not primary, but the gallbladder disease is definitely more common in persons with considerable coronary disease than in those without and vice versa (Walsh, Bland, Taquini and White, 1941). This association is to be attributed not to a mutual causative effect but to some common factor dependent largely on the aging process in the type of persons affected. Finally, even in the later years of life, nervousness and neurocirculatory asthenia may occur to exaggerate the symptoms of coronary heart disease and mental depression is frequently precipitated by the disability attending angina pectoris and particularly by the acute illness of myocardial infarction and the long but necessary convalescence, especially in the case of a strenuous middle aged professional or business man never ill before.

**Treatment** *Rest* Of prime importance is limitation of activity to suit each individual case. For acute myocardial infarction such rest should be more or less complete for a few weeks; more will be said about this below. For angina pectoris decubitus the rest should be almost as complete until the condition ameliorates, since acute coronary thrombosis is almost invariably the cause even though myocardial infarction may not follow. Even for angina pectoris on effort alone, it is often well at the onset to prescribe rest at home, though not in bed, until it is possible to appraise the situation adequately to determine the degree of chronicity of the disease and to plan future action.

**Drugs** There is no specific treatment for coronary heart disease per se.

unless it is due to syphilis a rare cause except for the quick relief of acute coronary insufficiency (angina pectoris) by the nitrites. The iodides which have been used empirically for general arteriosclerosis appear clinically to be inert although experimental animals have been protected somewhat from atherosclerosis induced by high cholesterol diets when given potassium iodide. A definite increase of the coronary flow by vasodilatation has been reported experimentally from the use of theobromine and especially theophylline ethylene diamine (aminophylline) and occasionally favorable effects on angina pectoris and dyspnea have been noted clinically after the use of these drugs. Their trial is justified but unless improvement is noted in the course of a week or two their continuance is not worthwhile; they are more likely to be effective when the coronary arteries are still able to dilate than in the case of rigid tubes. They may be administered by mouth in the dose of 10 gr 0.6 gm of theobromine (or 15 gr 1 gm of theobromine sodium salicylate Diuretin) three times daily, or preferably of 1½ to 3 gr 0.1 to 0.2 gm of theophylline ethylene diamine (aminophylline) three to five times a day. The theophylline ethylene diamine (aminophylline) may be much more effectively given intravenously (0.24 gm in ampoule) or by suppository two or three times daily over short periods of time; the intramuscular injection is often painful.

Other drugs which have been recommended for the treatment of coronary atherosclerosis and for their effects on the heart have been in general disappointing in fact often inert. Atropine was introduced hopefully to counteract a possible vagal factor in the production of coronary heart disease in man having been shown to be effective in dogs but its value has not been demonstrated. Choline and other lipotropic agents have been most recently used to delay prevent or even reverse somewhat the atheromatous process; they are effective in certain animals especially the rabbit but they have not yet passed in man beyond the experimental stage. Papaverine has been somewhat helpful in reducing the symptoms in particular the pain in coronary heart disease in the dosage of 0.03 to 0.09 gm (½ to 1½ gr) of the hydrochloride by subcutaneous injection twice daily or 0.09 to 0.20 gm (1½ to 3 gr) by mouth four times a day (Elek and Katz 1942) but it is often disappointing. Testosterone has little or no value unless there is a specific endocrine need thereof. The same is true of vitamin E and other vitamins. Tissue extracts in general have been of little value. Cactus is inert. Cobra venom has been recommended for intractable pain but has not become established.

One of the newly introduced drugs for the prophylaxis of angina pectoris apparently by the production of vasodilatation is khelin an active principle from the seeds of visnaga a plant growing in the Eastern Mediterranean area given in the dosage of 100 mg intramuscularly daily or 50 mg by mouth one to three times a day (Anrep et al 1947 1949 Armbrust and Levine 1950) in larger dosage this drug may cause nausea although its therapeutic effect has seemed favorable it is often toxic and needs further appraisal before widespread routine adoption.

Perhaps the most useful drugs to date for obstinate severe angina pectoris

both introduced to depress thyroid function have been thiouracil or better methylthiouracil (0.2 to 0.6 gm daily) and irradiated iodine to accomplish a medical thyroidectomy (Blumgart Freedberg et al 1948 1950) The latter procedure offers the greater promise with less hazard of the first 18 cases tried (of coronary or myocardial insufficiency more commonly the former) 6 have proved to be highly successful and 6 others improved while 6 were failures the dosage has averaged about 50 millicuries divided into 2 or 3 weekly administrations in water by mouth an average of 5 to 6 weeks elapsing before noticeable relief accompanying a drop of basal metabolic rate which is kept from descending too far by small amounts of thyroid

*Of prime import is the fact that in many cases there slowly, but spontaneously develops an adequate collateral coronary circulation and while that is going on nitrites in particular nitroglycerine (0.3 to 0.6 mg or 1/200 to 1/100 gr) and erythrol tetranitrate (15 to 30 mg or ¼ to ½ gr) may be used often very effectively prophylactically as needed or regularly to tide over many weeks or months of trouble during which care should be exercised to avoid undue strain physical or emotional I have found this procedure often the best of all*

For the immediate therapy of angina pectoris the nitrites are most useful for congestive failure as evidenced by dyspnea or edema (pulmonary or systemic) digitalis and diuretics (see Chapter 30) for coronary thrombosis with myocardial infarction and cardiac asthma morphine and if there is not adequate relief thereby a trial of oxygen by inhalation or of aminophyllin by vein, for ventricular paroxysmal tachycardia quinidine and for atrial fibrillation digitalis or quinidine In the case of coronary thrombosis it may be necessary to give large amounts of morphine even intravenously to control the pain often as much as ½ to 1 gr in divided doses in the course of a few hours or caffeine for collapse It is wise however to give no more morphine or its derivatives than is absolutely necessary because of the nausea the strain of vomiting constipation and the depression that commonly result If morphine does not in some cases control the very prolonged pain of myocardial infarction it is reasonable to try the effect of oxygen inhalation or of aminophyllin intravenously or of papaverine (0.2 gm 3 gr by mouth or 0.1 gm 1½ gr intramuscularly) these measures are usually disappointing but some times they help A ration of 0.2 gm (3 gr) of quinidine sulfate every 4 to 6 hours during the first 2 weeks of acute myocardial infarction or in cases of angina pectoris decubitus may prevent ventricular tachycardia and fibrillation it should be used routinely as a measure to reduce mortality in coronary heart disease (Borg 1939)

All of the various nitrites act by their vasodilating effect either directly to improve the coronary circulation by increasing its volume or indirectly by decreasing peripheral arterial resistance to relieve the work of the heart or more probably by both of these actions The most potent and rapid in effect of all the nitrites is the volatile *amyl nitrite* introduced by Brunton in 1867 It is inhaled from a small glass container (pearl or ampoule) broken at the

moment it is needed usually the amount in each container is 2 or 3 minims (0.12 to 0.18 cc). Inhalation causes in a few seconds flushing of the face, pounding of the pulse in the head and all over the body and relief of the angina pectoris. If inhalation is long continued, dizziness and a disagreeable headache may result. *Nitroglycerine* (glyceryl trinitrate, glonoin or trinitrin) introduced by Murrell in 1879 is after amyl nitrite the next most rapidly potent nitrite being absorbed in a minute or two with relief of angina pectoris and with the production of symptoms and signs of vasodilatation. It is best taken in the form of a quickly soluble tablet containing 1/200 gr (0.0003 gm) of nitroglycerine crushed and held in the mouth for rapid absorption. It must be reasonably soft, fresh and potent for sometimes the tablets are hard or become old and relatively inert. If the dose of 1/200 gr is ineffective 1/100 gr may be used but it is better to try first the smaller dose in any given case since it is often sufficient and does not produce so many disagreeable reactions—flushing, headache, pounding pulse, faintness and even syncope—to which some persons are subject. Even smaller doses 1/400 gr (0.00015 gm) or less are sometimes adequate especially for prophylactic use (see below).

Nitroglycerine is in most respects preferable to amyl nitrite in the treatment of an attack of angina pectoris for it is easier to carry and to use (not requiring the breaking of a glass container) is effective enough without being disagreeably and unnecessarily potent and its lower cost favors its constant use when needed rather than its reservation for rare occasions. Less important is *sodium nitrite* introduced by Hay in 1883 which in the dose of 1/2 to 1 gr (0.03 to 0.06 gm) in tablet form by mouth is rather slow in its effect requiring five to ten minutes but has the advantage of a longer continued effect (an hour or more) hence it can be used somewhat in a prophylactic way. For immediate therapy it is far inferior to nitroglycerine and amyl nitrite its actual effect is however similar. Next comes *erythrol tetranitrate* introduced by Bradbury in 1895 taken in 1/4 to 1/2 gr (0.015 to 0.03 gm) doses in tablet form by mouth it is more valuable than sodium nitrite because its effect lasts for several hours it is very slow in its action taking fifteen to thirty minutes to produce the usual nitrite effect. *Mannitol hexanitrate* introduced by Bradbury in 1895 and *mannitol pentanitrate* introduced by Marshall and Wigner in 1902 rarely used in the past have been recently revived they are taken in 1 gr (0.06 gm) doses in tablet form are very slow in their action requiring one hour to produce full effect but they continue to be effective for five or six hours. Finally *octyl nitrite* a liquid less volatile and effective than amyl nitrite has recently been introduced rather to be used prophylactically than in the direct treatment of an attack of angina pectoris administered by inhalation it requires 30 seconds for its effect which lasts about 20 minutes it has not established itself as at all preferable to the nitrites already in use. The last nitrites mentioned are primarily for prophylactic use erythrol tetranitrate being preferable although expensive and likely to give rise as are also the other preparations to obstinate and disagreeable headaches. The following table summarizes the speed and duration of action of the various nitrites.



Table 10

## THE SPEED AND DURATION OF ACTION OF VARIOUS NITRITE DRUGS

<i>Preparation</i>	<i>Speed of action</i>	<i>Duration of effect</i>
Amyl nitrite	A few seconds (10)	A few minutes (10)
Octyl nitrite	30 seconds	20 minutes
Nitroglycerine	1 to 2 minutes	30 minutes
Sodium nitrite	5 to 10 minutes	1 to 2 hours
Erythrol tetranitrate	15 minutes	3 to 4 hours
Mannitol hexanitrate or pentanitrate	30 minutes	4 to 5 hours

The most effective drug after the nitrites is *alcohol* it was used routinely one hundred years ago before the introduction of the nitrites and even now when the nitrites are not available an ounce or two of whisky brandy or rum may give quite rapid relief from angina pectoris usually in the course of a very few minutes. However inasmuch as a paroxysm of angina pectoris is likely to subside before alcohol exerts its full effect these various beverages are more useful in prevention than in treatment and inasmuch as alcoholism as a habit may be established by this procedure the prophylactic use of nitroglycerine is much to be preferred. It should be added that although heavy drinkers seem to show little atheroma the moderate or even the considerable use of alcohol does not protect against coronary heart disease in middle age. I have encountered a good many patients who have proved this point.

Other drugs for the immediate treatment of angina pectoris are either less effective than the nitrites and alcohol or inadvisable. Ether and chloroform were sometimes used in treatment in place of alcohol in the early days before the introduction of the nitrites but now there is little place for them they may be effective in severe prolonged attacks. Bromides are of little use except to calm nervous excitement. Morphine is too slow in its action and is far less effective than the nitrites it should be avoided in the vast majority of cases and simply reserved for severe long continued pain not relieved by an effective nitrite and generally due to myocardial infarction. Serious drug addiction and psychoneuroses have frequently followed the unwise use of opiates in the treatment of angina pectoris. Digitalis and strophanthin do not relieve angina pectoris in fact they may aggravate it but they can be used without fear to relieve congestive heart failure or to control the ventricular rate of atrial fibrillation in spite of the presence of attacks of angina pectoris.

*Diet* Much has been said and written about the relationship of diet to coronary atherosclerosis (the basis of 99 per cent of coronary heart disease) but most of it is still conjecture and opinion. It is certainly true that the deposition of cholesterol in the coronary arterial intima is the fault with which we are concerned that cholesterol foods are richly ingested in this country and that coronary patients and candidates are prone to have high cholesterol contents in their blood. But as stated earlier in this chapter under *Etiology* doubtless much if not the major part of this blood cholesterol is

of endogenous origin associated with metabolic processes and not exogenous. The total calories of a rich diet may well be most important of all.

In the present state of our knowledge it would seem wise to maintain a diet of moderation low in cholesterol foods (especially eggs butter cream and cheese) in robust persons with coronary heart disease or who look like candidates. It probably is not necessary or wise to exclude these fats completely but it does appear advisable to treat obesity to recommend limited caloric intake (according to activity) to avoid large or rich meals and perhaps to limit also heavy use of tobacco. Alcoholic beverages may be permitted provided their caloric values are taken into consideration but they do not have any special virtues.

Control of various activities care of bowels and sometimes hospital or sanitarium treatment are necessary in the therapy of coronary heart disease and its complications. Much attention may be needed in a chronic case to prevent the occurrence or recurrence of serious complications but each patient must be considered individually on each occasion and not be made to follow any set rules. It need only be said that any activity or strain of doubtful effect should be avoided unless the patient is thereby too depressed or unhappy. A balance must always be sought between too much and too little restriction of life not only from the standpoint of longevity but also from that of happiness.

*Acute coronary thrombosis* must be regarded more seriously than most cardiac conditions and careful rest for weeks or months (a minimum of three to four weeks) should be prescribed in order to assure as sound a healing of the myocardial infarct as possible with a very gradual and careful convalescence (a minimum of one month after completing the rest period) by wise treatment at the start. Life may doubtless be prolonged for many years in some cases. At times shortly after coronary thrombosis when the patient is feeling well and therefore possibly too active sudden death from cardiac rupture or other cause may occur sometimes however this accident is not preventable. Sutton and Davis (1931) made the interesting observation that in dogs rest for six days after the production of cardiac infarction permitted the formation of a small well-contracted scar without thinning of the wall of the ventricle while exercise within three days of the infarction produced aneurysmal bulging of the ventricular wall with a thin scar. The absolute need of complete rest for two weeks after a large acute myocardial infarction in man has been clearly demonstrated by the finding of rupture of the heart during the first twelve days in 16 or 73 per cent of 22 psychopathic patients in contrast to only 10 cases or 9.5 per cent of 105 patients in the wards of a general hospital (Jettler and White 1944 Friedman and White 1944).

As the result of experience during the last twenty five years I have found that a very satisfactory plan of treatment for the average case of acute myocardial infarction is one month of full rest (the first fortnight very quiet to avoid so far as possible serious complications in particular dilatation and rupture of the heart during the critical period of softening of the wall and the beginning of the laying down of the scar) one month of gradually increasing

activity (the first week in a chair a little more each day the second week walking on the level increasing distances the third week going slowly over the stairs once a day and the fourth week going out for short daily rides weather permitting) and a third month if possible (although this is not always essential) to consolidate the recovery nervously as well as otherwise. One may need to lengthen or shorten these three periods of the convalescence as circumstances demand. It is of importance to realize that the heart may recover more rapidly than the depressed mental state which is so often a complication. Too long a stay in bed or too long a total convalescence is bad for the morale and the general health. During the last two decades the pendulum has swung from one extreme to the other with respect to the length of time at full rest and of total convalescence from two or three months of the former and six months to a year of the latter to a few days only at rest and a few weeks only away from work. The wisest course is doubtless to avoid both these extremes.

An important consideration in the treatment of acute myocardial infarction which has been much debated is that of bed rest versus rest in a chair. In mild cases with small infarcts there is no reason why the patient may not sit in a comfortable chair by the bedside even during the first week avoiding however physical exertion. Also if a patient is very ill and has orthopnea or otherwise is uncomfortable recumbent he may be lifted into a suitable large chair or better still use a chair bed (see Chapter 30). In any case a bedside commode for bowel movements is for many persons better than a bedpan since its use is much less of a strain. Bathroom privileges are best reserved until after the first fortnight. And finally quiet exercise of the legs daily while still otherwise at full rest is advisable to help prevent leg vein thrombosis.

A limited diet to maintain a low basal metabolic rate during the process of healing of the infarct has been advised also (Master et al. 1935) but this in extreme degree is usually unnecessary and probably at times unwise. A light mixed diet of 1 800 to 2 100 calories in 4 or 5 small meals a day is a good plan. In the case of an obese patient a low calorie diet is in order, and if congestion threatens the diet should be low in sodium.

*Other measures* In recent years several new measures of treatment have been introduced to control certain manifestations or complications of coronary heart disease. Paravertebral alcohol injections of the sympathetic nerve connections to the heart have been largely supplanted by sympathectomy itself but this procedure too is now rarely indicated in part because of the reversibility of the coronary heart disease in time in the majority of cases even of severe angina pectoris (including the decubitus type) by patience and medical therapy in particular free use of the nitrites often tiding over the disagreeable and hazardous period of serious illness and in part because of the superiority of irradiated iodine therapy (mentioned above) in the most obstinate cases. The principle of total thyroidectomy ingeniously introduced in 1933 and soon abandoned has been recently revived as the medical measure just referred to. Much direct surgery on the heart has been attempted to bring new blood supply by constructing anastomoses to the coronary circulation. Beck has

been a leader in this field (1935 and since) and although many of the results have been disappointing especially in establishing pericardial adhesions (also produced via the omentum by O'Shaughnessy 1937 and via powdered substances) new trials are in progress consisting most recently of grafting a systemic (e.g. brachial) vein into the coronary sinus and later on, partially occluding the sinus. Fauteux (1941, 1946 and 1948) performed much original work on the heart to improve the coronary circulation by ligating the great cardiac vein and to reduce the hazard of ventricular fibrillation by coronary neurectomy but these procedures though promising are still hazardous in man.

Anticoagulants both heparin and dicoumarin but especially the latter have been in the last decade introduced in coronary heart disease for two purposes. Complications of thrombosis and embolism both pulmonary (chiefly from leg vein clots) and systemic from intracardiac thrombi mostly over a healing infarct have been distinctly diminished by anticoagulant therapy begun at the earliest stage of acute coronary thrombosis with myocardial infarction. With or without initial heparin (which may prove wise if readily available) Dicumarol is given the first day usually in the dosage of 200 mg after a test of the prothrombin time has shown no abnormal delay and provided daily tests of the prothrombin time of the patient's serum can be accurately determined. A daily dosage of 50 to 100 mg or none at all is given thereafter during the next three or four weeks to maintain a prothrombin concentration of 20 to 50 per cent of the normal. Wright not long ago (1948) analyzed 800 cases of acute myocardial infarction half of whom received Dicumarol and half observed as controls. The mortality was 13 per cent in the treated patients and 23 per cent in the controls and there were thromboembolic complications in only 13.1 per cent of the treated cases in contrast to 41.8 per cent of the controls. A new oral anticoagulant more rapidly acting than Dicumarol called Tromexan is now on trial (Wright 1951).

Less amenable to proof the other purpose for anticoagulant therapy in coronary heart disease has been to prevent or delay coronary thrombosis itself. This is still in the experimental stage and may prove to be both impractical and ineffective. It may have to be continued for years and during its use the blood must be tested frequently (daily or every few days) to be safe for the hazard of hemorrhage exists as well as of ineffective dosage. To combat serious effects of anticoagulants certain measures have been introduced the most effective is vitamin K<sub>1</sub> oxide (0.5 gm or more intravenously) whole blood transfusions have yielded minor temporary benefit (James et al 1948). As a matter of fact, vitamin K has even been recommended in the treatment of coronary disease in certain cases with the idea of preventing hemorrhage in the coronary wall (Doles 1947) but confirmation of this is still lacking.

Last but not least one must treat the state of shock which not rarely complicates acute coronary thrombosis or acute myocardial infarction. Simple measures of absolute rest and quiet and nursing care with strong coffee by mouth and aminophyllin intravenously may suffice in mild cases but in serious shock

something radical may be needed to save a life. Here transfusion with care under close observation may be helpful—up to 250 or 300 or more cc slowly given watching carefully for overloading of the veins pulmonary and systemic in the face of a weak heart muscle. Plasma may be given instead of whole blood.

Finally in all the therapy of coronary heart disease one must not lose sight of the very important facts (1) that the heart itself possesses a striking recuperative capacity no matter what is done but (2) that great care in all details of physical activity and nervous strain in exposure to weather and in eating and other habits may be essential for survival over periods of acute or subacute trouble.

**Differential diagnosis.** Chronic coronary heart disease is often very difficult to discover and in the stage of congestive failure with arrhythmia may be hard to distinguish from rheumatic heart disease or thyrotoxic effects. The age of the patient a history of angina pectoris the usual absence of characteristic murmurs of chronic valvular disease the usual absence of much cardiac enlargement the finding of tortuosity of the aorta by roentgen ray and of intraventricular block or other even more specific coronary electrocardiographic patterns help to establish the correct diagnosis. Myxedema too has been occasionally confused with coronary heart disease on the basis of the electrocardiograms which with abnormal *T* waves and low voltage of the *QRS* waves may be indistinguishable in the two chronic diseases, however, the appearance and symptoms of the patient readily reveal the myxedema confirmed by the very low basal metabolic rate. These diseases may coexist.

Acute coronary occlusion with cardiac infarction has been frequently confused in the past with *acute abdominal disease* such as acute indigestion gall stones and perforated peptic ulcer and laparotomy has been done in some cases by mistake. Although position of the pain fever leukocytosis and gastrointestinal symptoms like vomiting may be common to the two conditions there are usually enough differences to make the distinction fairly certain. The most important point in this differentiation is the past history in the one case a story of angina pectoris or other cardiac symptoms or signs and in the other a record of indigestion or colic. Other signs and symptoms of importance in differentiating coronary thrombosis and acute abdominal disease are first to be found in the cardiac examination which may show characteristic abnormalities namely dilatation poor sounds pericardial friction rub and specific electrocardiographic findings such as *T* wave changes and intraventricular or atrioventricular block. Secondly the abdominal examination may show masses definitely localized tenderness or spasm or there may be jaundice or bleeding from the gastrointestinal tract. Thirdly the pain in myocardial infarction is more often high under the sternum or both substernal and epigastric rarely epigastric alone and is very frequently referred to the arms especially the left. And fourthly the victims of coronary thrombosis are preponderantly elderly or middle aged men while acute abdominal disease is common in middle aged women as well as in men. Despite the greatest care however if

a diseased gallbladder is unusually high in position, acting almost like an intrathoracic organ it may be mistaken for an infarcted heart in the presence of some coincident coronary heart disease

There are four other conditions that are especially likely to be confused with acute coronary occlusion they are acute pericarditis, dissecting aortic aneurysm, pulmonary embolism and mediastinal emphysema. The first *pericarditis* is commonly misinterpreted particularly in young adults in whom the error can be serious both from the standpoint of prognosis and from that of treatment and of the plan of life the differentiation is as a rule easy in two particulars: precordial pain that is felt preponderantly or only on respiration and little if at all when the breath is held is due as a rule to acute pleuropericarditis and not to myocardial infarction and an electrocardiogram that shows very little or very transient or unusual abnormalities (such as transient elevation of the *ST* segments or flattening or inversion of the *T* waves in all leads) points much more to pericarditis than to myocardial infarction. The youth of the patient is often a clue but the severe long continued pain, fever, leukocytosis and pericardial friction rub may easily lead one astray. *Dissection of the aortic wall* is to be distinguished by the very abrupt onset of most severe pain (not working up to a crescendo as in most cases of coronary thrombosis) the reference of the pain almost invariably to the back and often down to the legs the evidence of obstructed circulation in the branches of the aorta especially the iliac and femoral arteries the relatively normal electrocardiogram and the almost constant presence of chronic hypertension. In the case of *pulmonary embolism* there is usually a story of recent surgical operation or injury association with thrombophlebitis more often severe dyspnea or prostration than severe pain and normal or characteristic electrocardiogram (if the acute cor pulmonale is present) (see Chapter 20) the chief difficulty with respect to this particular differential diagnosis is that both conditions not rarely occur together in the same patient one leading to the other. *Mediastinal emphysema* (Hamman 1937) is fortunately very rare but it may be very confusing and give rise temporarily (that is for a few hours) to symptoms and signs that simulate acute myocardial infarction there may be intense substernal pain and a state bordering on shock the heart sounds may be weakened or attended by crepitations which might casually be confused with friction there may be a temporary change in the electrocardiogram and slight fever and leukocytosis but the differentiation should not be difficult if this condition is borne in mind because of the rapid clearing of the signs and symptoms and the usual finding of air in the mediastinum or even under the skin

Besides these five conditions with which acute coronary occlusion may readily be confused there are many other diseases which may more or less uncommonly be mistaken for it. Herrick (1935) listed 28 different conditions which he had himself seen mistaken for coronary thrombosis they are as follows: paroxysmal angina pectoris, cardiac arrhythmia, cardiac neurosis, neurocirculatory asthenia, malingering, acute pericarditis, syphilitic aortitis with and without aneurysm, dissecting aortic aneurysm, pleurosy, pneumonia /

carcinoma of bronchus and lung massive collapse of the lung pneumothorax pulmonary embolism herpes zoster, arthritis of costochondral articulation shoulders and spine bursitis gallstones peptic ulcer, carcinoma of stomach or duodenum acute gastritis spastic colitis diaphragmatic hernia tabetic crisis and impending diabetic coma Diaphragmatic flutter might be added to this list

Finally angina pectoris as a symptom of coronary heart disease may like wise be overdiagnosed most commonly when there is indigestion with cardio spasm (with or without a hiatus or diaphragmatic hernia), neurocirculatory asthenia or cardiac arrhythmia Angina pectoris ■ a characteristic symptom of coronary insufficiency due primarily to coronary atherosclerosis has been well described earlier in this chapter especially in the quotation from Heber den It is closely simulated only by spasm of esophagus or cardia of stomach (cardiospasm) from which it is to be as a rule readily distinguished by its relationship to effort rather than eating and by its more rapid response to nitroglycerine

If in rare cases who are not gravely ill there is serious doubt about the diagnosis of coronary insufficiency recourse may be made to exercise tests such as customary walking or stair-climbing or Master ■ two-step test or to Levy's anoxemia test

## BIBLIOGRAPHY

THE CORONARY CIRCULATION CORONARY ARTERY DISEASE CORONARY HEART DISEASE ANGINA PECTORIS MYOCARDIAL INFARCTION

SEE ALSO REFERENCES UNDER CHAPTER 9 ELECTROCARDIOGRAPHY AND 25 MYOCARDIAL DISEASE

### General Etiology and Diagnosis

- Allan G A "Diseases of the Coronary Arteries" *Brit M J* 1928 II 232  
 Allbutt C *Diseases of the Arteries Including Angina Pectoris* Macmillan & Company Ltd London 1915 Vol II Section II  
 Baggenstoss A H and Keith H M "Calcification of Arteries of an Infant Report of Case" *J Pediat* 1941 XVIII 95  
 Black S "Case of Angina Pectoris with Remarks" *Memoirs of the Medical Society of London* 1795 IV 261 Letter to Thomas Percival and by him communicated to the Medical Society of London read March 10 1794  
 Bland E F White P D and Garland J "Congenital Anomalies of the Coronary Arteries Report of an Unusual Case Associated with Cardiac Hypertrophy" *Am Heart J* 1933 VIII 787  
 Boas E P "Angina Pectoris and Cardiac Infarction from Trauma or Unusual Effort" *J.A.M.A.* 1939 CXII 1887  
 Bonetus R *Sepulchretum* (Leonard Chouet Geneva 1679) Second edition (Mangetus) Cramer and Perachon Geneva 1700  
 Bradbury S "Thirty Years After Ligation of the Anterior Descending Branch of the Left Coronary Artery" *Am Heart J* 1942 XXIV 362  
 Breyfogle H S "The Frequency of Coexisting Gall Bladder and Coronary Artery Disease" *J.A.M.A.* 1940 CXIV 1434  
 Brown, C E and Richter I M "Medial Coronary Sclerosis in Infancy" *Arch Path* 1941 XXXI 449

- Clawson H J Incidence of Types of Heart Disease Among 30 265 Autopsies with Special Reference to Age and Sex *Am Heart J* 1941 XXII 607
- Cohnheim J and von Schulthess-Rechberg A Über die Folgen der Kranzarterienverschliessung für das Herz *Virch Arch f path Anat* 1881 LXXXV 503
- Duff G L Experimental Cholesterol Arteriosclerosis and Its Relationship to Human Arteriosclerosis *Arch Path* 1935 XX 81 and 259
- Ehrlich W de la Chapelle C and Cohn A E Anatomical Ontogeny B Man 1 A Study of the Coronary Arteries *Am J Anat* 1931 XLIX 241
- Fothergill J Further Account of the Angina Pectoris *M Observ & Inquiries* (Cadell London) 1776 V 252
- Gallavardin L *Les angines de poitrine* Masson et Cie Paris 1925
- Glendy R E Levine S A and White P H Coronary Disease in Youth Comparison of 100 Patients Under 40 with 300 Persons Past 80 *JAMA* 1937 CIX 1775
- Greene C W Nerve Control of Coronary Vessels with New Experimental Evidence for Pathways of Efferent Constrictor and Dilator Neurones in the Dog *Am J Physiol* 1935 CXIII 361
- Control of Coronary Blood Flow by Reflexes Arising in Widely Distributed Regions of the Body *Am J Physiol* 1935 CXIII 399
- Gross L *The Blood Supply to the Heart in Its Anatomical and Clinical Aspects* Paul B Hoeber Inc New York 1921
- Hall G E Experimental Heart Disease *Ann Int Med* 1939 XII 907
- Hamman L The Prognosis of Angina Pectoris *Am J M Sc* 1914 CLXVIII 786
- ✓ Heberden W Some Account of a Disorder of the Breast *M Tr Royal College of Physicians* London 1772 II 58 (The original mention of angina pectoris was made by Heberden in a lecture before the Royal College of Physicians in London in July 1768)
- Herapath C E K and Perry C B The Coronary Arteries in a Case of Familial Liability to Sudden Death *Brit M J* 1930 I 685
- Herrick J B On the Combination of Angina Pectoris and Severe Anemia *Am Heart J* 1927 II 351
- Hochrein M *Der Coronarkreislauf Physiologie Pathologie Therapie* Julius Springer Berlin 1932
- Huber K "Über den Einfluss der Kranzarterienerkrankung auf das Herz und die chronische Myocarditis" *Virch Arch f path Anat* 1882 LXXXIX 236
- Huchard H Records of 185 cases of coronary disease examined post mortem *Maladies du Cœur et de l'Aorte* 3rd ed Octave Doin Paris 1890 II 522
- Jenner E Letter on the relationship of coronary disease to angina pectoris in Parry's volume on *Syncope Anginosa* See below
- Keefer C S and Resnick W H Angina Pectoris a Syndrome Caused by Anoxemia of the Myocardium *Arch Int Med* 1928 LI 769
- Kowalczykowska J Todliche Herzbeutelblutung infolge Ruptur eines Kranzschlagaderzweiges *Virch Arch f path Anat* 1934 CCXCIH 464
- Leary T Pathology of Coronary Sclerosis *Am Heart J* 1935 X 328
- Coronary Spasm as a Possible Factor in Producing Sudden Death *Am Heart J* 1935 X 338
- Levy R L Bruenn H G and Kurtz D Facts on Disease of Coronary Arteries Based on a Survey of Clinical and Pathologic Records of Seven Hundred and Sixty-two Cases *Am J M Sc* 1934 CLXXXVII 376
- Levy R L Bruenn H G and Russell M G Jr Use of Electrocardiographic Changes Caused by Induced Anoxemia as Test for Coronary Insufficiency *Am J M Sc* 1939 CXCVII 241
- Lewis T "Pain in Muscular Ischemia Its Relation to Anginal Pain" *Arch Int Med* 1932 XLIX 713
- Angina Pectoris Associated with High Blood Pressure and Its Relief by Amyl Nitrite with a Note on Nothnagel's Syndrome" *Heart* 1931 XV 305
- Leyden E V "Ueber die Sclerose der Coronar Arterien und die davon abhängigen Krankheitszustände" *Ztschr f klin Med* 1883-4 VII 459 539
- Lian C H et al *L'Angine de Poitrine Formes Cliniques Traitement Médical et Chirurgical* Masson et Cie Paris 1932.



- Lisa J R and Brown C R "Arterial Disease of the Heart" *Ann Int Med* 1941 XIV 2147
- Mackenzie J "Angina Pectoris" *Oxford Medical Publications* Henry Frowde Hodder and Stoughton London 1923
- Manohar K D "Aneurysm of a Coronary Artery" *Arch Path* 1938 XXVI 1131
- Master A M "The Two-Step Test of Myocardial Function" *Am Heart J* 1935 X 495
- Morgagni J B *De Sedibus et Causis Morborum* Typographia Remondiniana, Venice 1761
- Moritz A R and Beck C S "The Production of a Collateral Circulation to the Heart II Pathological Anatomical Study" *Am Heart J* 1935 X 874
- Muller C "Angina Pectoris in Hereditary Xanthomatosis" *Arch Int Med* 1939 LXIV 675
- Nothnagel H "Angina pectoris vasomotoria" *Deutsch Arch f klin Med* 1867 III 309
- Parkinson J and Bedford D E "Cardiac Infarction and Coronary Thrombosis" *Lancet* 1928 I 4
- Electrocardiographic Changes During Brief Attacks of Angina Pectoris Their Bearing on the Origin of Anginal Pain *Lancet* 1931 I 15
- Parry C H *An Inquiry into the Symptoms and Causes of the Syncope Anginosa Commonly Called Angina Pectoris Illustrated by Dissections* (Containing an important letter from E Jenner) R Cruikshank Bath 1799
- Root H F Bland E F Gordon W H and White P D "Coronary Arteriosclerosis in Diabetes Mellitus A Postmortem Study" *JAMA* 1939 CXIII 27
- Snellen H A and Nanta J H "Zur Röntgendiagnostik der Koronarverkalkungen" *Fortschr a d Geb d Röntgenstrahlen* 1937 LVI 277
- Spillane J E and White P D "Atypical Pain in Angina Pectoris and Myocardial Infarction" *Brit Heart J* 1940 II 123
- Sternberg C "Zur pathologischen Anatomie der Angina pectoris" *Wien med Wchnschr.* 1924 LXXIV 2338
- Walsh B J Bland E F Taquini A C and White P D "The Association of Gall Bladder Disease and of Peptic Ulcer with Coronary Disease a Postmortem Study" *Am Heart J* 1941 XXI 689
- Wearn J T Mettler S H Klumpp T G and Zschiesche L J "The Nature of the Vascular Communications between the Coronary Arteries and the Chambers of the Heart" *Am Heart J* 1933 IX 143
- Weigert K "Ueber die pathologischen Gerinnungsvorgänge" *Virch Arch f path Anat* 1880 LXXIX 89
- White P D "The Prognosis of Angina Pectoris and of Coronary Thrombosis" *JAMA* 1926 LXXXVII 1525
- White P D and Bland E F "A Further Report on the Prognosis of Angina Pectoris and of Coronary Thrombosis A Study of Five Hundred Cases of the Former Condition and Two Hundred Cases of the Latter" *Am Heart J* 1931 VII 1
- White P D Bland E F and Miskall E W "A Long Follow up (12 to 23 Years) of the Prognosis of Angina Pectoris (497 Cases) Including That of Angina Pectoris Decubitus" *JAMA* 1943 CXXIII 801
- White P D and Camp P D "The Status Anginosus Induced by Paroxysmal Auricular Fibrillation and Paroxysmal Tachycardia" *Am Heart J* 1932 VII 581
- White P D and Jones T D "Heart Disease and Disorders in New England" *Am Heart J* 1928 III 302
- White P D and Mudd S G "Angina Pectoris in Young People" *Am Heart J* 1927 III 1
- Whiting W H "Angina Pectoris at the Age of Fourteen Associated with Congenital Rudimentary Right Coronary Artery and Rudimentary Posterior Cusp of Mitral Valve" *Am Heart J* 1937 XIV 104
- Wolkoff, K. "Über die Atherosklerose der Coronararterien des Herzens" *Beitr path Anat u - allg Path* 1929 LXXXII 555
- Ziegler E *Lehrbuch der allgemeinen und speciellen Anatomie und Pathogenese* Fischer Jena 1881

## Recent References (1944-1950)

- Ackerman R F Dry T J and Edwards J E Relationship of Various Factors to the Degree of Coronary Atherosclerosis in Women *Circulation* 1950 I 1345
- Adlersberg D and Parets A D Genetic Studies of 201 Persons with Hereditary Hypercholesterolemia (Thirty five Families and Twenty nine Individuals) *J Clin Investigation* 1949 XXVIII 767
- Alvord R M Coronary Heart Disease and Xanthoma Tuberosum Associated with Hereditary Hyperlipemia Study of Thirty Affected Persons in a Family *Arch Int Med* 1949 LXXXIV 1002
- Barr II P The Relation of Cholesterol Metabolism to the Pathogenesis of Atherosclerosis Talk delivered at the New York Academy of Medicine February 20 1951
- Bing R J and associates Catheterization of the Coronary Veins and the Measurement of Coronary Blood Flow in Man *J Clin Investigation* 1948 XXVII 525
- Björck G Anoxemia and Exercise Tests in the Diagnosis of Coronary Disease *Am Heart J* 1946 XXXII 689
- Bloch K "The Intermediary Metabolism of Cholesterol" *Circulation* 1950 I 214
- Boss E P Parets A D and Adlersberg II "Hereditary Disturbance of Cholesterol Metabolism A Factor in the Genesis of Atherosclerosis" *Am Heart J* 1948 XXXV 611
- Burchell H B Prust R D and Barbes A R The Stress and the Electrocardiogram in the Induced Hypoxemia Test for Coronary Insufficiency *Am Heart J* 1948 XXXVI 373
- Cain E F and Ware E R "Diaphragmatic Flutter with Symptoms Suggesting Angina Pectoris" *JAMA* 1946 CXXXI 1058
- Dack S Stone J Grishman A and Master A M Differential Diagnosis of Diaphragmatic Hernia and Coronary Heart Disease *Bull New York Acad Med* 1948 XXIV 396
- Davidson J II Meyer W and Kendall F F Effect of Choline Upon Experimental Canine Arteriosclerosis *Circulation* 1951 III 332
- Dock W Coronary Atherosclerosis *JAMA* 1946 CXXXI 875
- Geisinger E "The Mural Coronary" *Am Heart J* 1951 XLI 359
- Gertler M M Garn S M and Bland E F Age Serum Cholesterol and Coronary Artery Disease" *Circulation* 1950 II 517
- Gertler M M Garn S M and Lerman J "The Interrelationships of Serum Cholesterol Cholesterol Esters and Phospholipids in Health and in Coronary Artery Disease" *Ibid* 1950 II 205
- Gertler M M Garn II M and Sprague II B "Cholesterol Cholesterol Esters and Phospholipids in Health and in Coronary Artery Disease II Morphology and Serum Lipids in Man" *Ibid* 1950 II 380
- Gertler M M Garn S M and White P D Diet Serum Cholesterol and Coronary Artery Disease *Ibid* 1950 II 696
- Gertler M M Garn S M and White P D with the advice and assistance of Bland E F Lerman J Levine II A and Sprague II B *A Study of One Hundred Young Persons after Myocardial Infarction with Especial Reference to Sex Body Build Metabolism and Biochemistry As Compared with One Hundred and Forty six Controls* The Commonwealth Fund New York 1951
- Goffman J W Jones H B Lindgren F T Lyon T P Elhott II A and Strisower B Blood Lipids and Human Atherosclerosis *Circulation* 1950 II 161
- Gregg D E *Coronary Circulation in Health and Disease* Lea & Febiger Philadelphia 1950
- Habbe J E and Wright H H Roentgenographic Detection of Coronary Arteriosclerosis *Am J Roentgenol* 1950 LXIII 40
- Hamilton J B "A Relationship of Maleness to Shortness of the Lifespan and to Certain Pathological Conditions" *J Gerontol* 1948 III 7
- Hueper W C "Arteriosclerosis" *Arch Path* 1944 XXCVIII 162 245 350 and 1945 XXXIX 51 117
- Jokl E and Greenstein J "Fatal Coronary Sclerosis in a Boy of Ten Years" *Lancet* 1944 II 659

- Katz L N Stamler J and Horlick L "Cholesterol Metabolism in Health and Disease Its Relationship to Arteriosclerosis" *Am Pract & Dig Treat* 1950 I 461
- Keys A Mickelsen O Miller E V O and Chapman C H "The Relation in Man Between Cholesterol Levels in the Diet and in the Blood" *Science* 1950 CXII 79
- Lansing A I Alex M and Rosenthal T B "Calcium and Elastin in Human Arteriosclerosis" *J Gerontol* 1950 V 112
- Leary T "Crystalline Ester Cholesterol and Atherosclerosis" *Arch Path* 1949 XLVII 1
- Master A M Dack S Horn H Freedman B I and Field L E "Acute Coronary Insufficiency Due to Acute Hemorrhage: An Analysis of One Hundred and Three Cases" *Circulation* 1950 I 1302
- Menten M L and Fetterman G H "Coronary Sclerosis in Infancy: Report of Three Autopsied Cases Two in Siblings" *Am J Clin Path* 1948 XVIII 805
- Minkowski W L "The Coronary Arteries of Infants" *Am J M Sc* 1947 CCXIV 623
- Montgomery G E Jr Dry T J and Gage R P "Further Observations on the Prognosis in Angina Pectoris Due to Coronary Sclerosis" *Minnesota Med* 1947 XXX 162
- Moragues V Bawell M B and Shrader E L "Coronary Embolism: Review of the Literature and Report of a Unique Case" *Circulation* 1950 II 434
- Moreton J R "Physical State of Lipids and Foreign Substances Producing Atherosclerosis" *Science* 1948 CVII 371
- Okey R "Cholesterol Content of Foods" *J Am Dietet A* 1945 XXI 341
- Paul O Sweet R H and White P D "Coronary Arteriovenous Fistula" *Am Heart J* 1949 XXXVII 441
- Pickering G W and Sanderson P H "Angina Pectoris and Tobacco" *Science* 1945 V 275
- Porter W B "Probably Grave Significance of Premature Beats Occurring in Angina Pectoris Induced by Effort" *Am J M Sc* 1948 CCXVI 509
- Rabson S M and Helpern M "Sudden and Unexpected Natural Death II Coronary Artery Sclerosis" *Am Heart J* 1948 XXXV 635
- Scott E H "Aneurysm of the Coronary Arteries" *Am Heart J* 1948 XXXVI 403
- Simms H S and Parshley M S "Studies on the Fat Depositing Mechanism" *Am Heart J* 1948 XXXV 859
- Simms H S Parshley M S Pitt R W and Fulton J B "Further Studies on the Fat Depositing Mechanism" *Am Heart J* 1948 XXXVI 469
- Sperstein M D Chaikoff I L and Chernick S S "Significance of Endogenous Cholesterol in Arteriosclerosis: Synthesis in Arterial Tissue" *Science* 1951 CXIII 747
- Smith T M "Coronary Atherosclerosis in the Negro" *J Nat M A* 1946 XXVIII 193
- Stewart A Kendall F E and Bevans M "Production of Arteriosclerosis in Dogs by Cholesterol and Thiouracil Feeding" *Am Heart J* 1949 XXXVIII 34
- Stewart H J Horger E L and Sorenson C W "Experience with the Anoxemia Test in Patients with Typical Angina of Effort and in Patients with Atypical Pain Which May Be Due to Coronary Insufficiency" *Am Heart J* 1948 XXXVI 161
- Stryker W A "Arterial Calcification in Infancy with Special Reference to Coronary Arteries" *Am J Path* 1946 XXII 1007
- Talbot N B Butler A M Pratt E L MacLachlan E A and Tannheimer J "Progeria: Clinical, Metabolic and Pathologic Studies on a Patient" *Am J Dis Child* 1945 LXIX 267
- Vakil R J "A Study of Coronary Heart Disease in India (250 Cases of Coronary Heart Disease in a Total Medical In Patient Population of 30 104 Patients at the King Edward Memorial Hospital Bombay)" *Indian Heart J* 1949 I 201
- White P D and Ferrero C "Research Problems in Coronary Heart Disease" *Ann Int Med* 1949 XXXI 33
- White P D "Coronary Heart Disease in Midcentury With a Note Concerning Its Military Importance" *US Armed Forces Med J* 1951 II 357
- "The Relative Incidence of the Etiologic Types of Heart Disease in New England Compared to That of 25 Years Ago: An Analysis of 3000 Cases" 1951 in press

- Wilens S L "Resorption of Arterial Atheromatous Deposits in Wasting Disease" *Am J Path* 1947 XXIII 793
- Yater W M Traut A H Brown W G Fitzgerald R P Geisler M A and Wilcox H B "Coronary Artery Disease in Men Eighteen to Thirty nine Years of Age" *Am Heart J* 1948 XXXVI 334 481 683
- Zuckermann R Velázquez T Bisteni A and Ortiz Marquez J "Flebotrombosis y tromboflebitis coronarias" *Arch del Inst de Cardiol de Mexico* 1950 XX 565 and 610

### Treatment

- Beck C S "Development of New Blood Supply to Heart by Operation" *Ann Surg* 1935 CII 801
- Blumgart H L Levine H A and Berlin H B Congestive Heart Failure and Angina Pectoris The Therapeutic Effect of Thyroidectomy on Patients Without Clinical or Pathologic Evidence of Thyroid Toxicity *Arch Int Med* 1933 LI 866
- Bradbury J H "The Bradshaw Lecture on Some New Vaso-Dilators" *Brit M J* 1895 II 1213
- Brown M G and Riseman J E F "The Comparative Value of Purine Derivatives in the Treatment of Angina Pectoris" *JAMA* 1937 CIX 256
- Brunton T L "On the Use of Nitrite of Amyl in Angina Pectoris" *Lancet* 1867 II 97 (This paper reports the introduction of amyl nitrite as a therapeutic measure in angina pectoris)
- Cutler E C and Hoerr S O "Total Thyroidectomy for Heart Disease Five Year Follow up Study" *Ann Surg* 1941 CXIII, 245
- Elek B R and Katz L N "Some Clinical Uses of Papaverine in Heart Disease" *JAMA* 1942 CXX 434
- Evans W and Hoyle C "The Comparative Value of Drugs Used in the Continuous Treatment of Angina Pectoris" *Quart J Med* 1933 II 311
- Fautert M., and Palmer J H "Treatment of Angina Pectoris of Atheromatous Origin by Ligation of Great Cardiac Vess. *Canad M A J* 1941 XLV 295
- Feil H and Beck C S "Coronary Sclerosis and Angina Pectoris Report of Thirty Patients Treated by the Beck Operation" *J Thoracic Surg* 1941 X 529
- Freedberg A S and associates "Octyl Nitrite in the Treatment of Angina Pectoris" *Am Heart J* 1941 XXII 519
- Gold H and associates "The Xanthines (Theobromine and Aminophylline) in the Treatment of Cardiac Pain" *JAMA* 1937 CVIII 2173
- Hay M "Nitrite of Sodium in the Treatment of Angina Pectoris" *Practitioner* London, 1883 XXX 179 (This paper reports the introduction of sodium nitrite as a therapeutic measure in angina pectoris)
- Hoyle C and Evans W "Therapeutic Effect of a Period of Rest in Bed in Angina Pectoris (Angina of Effort)" *Lancet* 1934 I 563
- Jonnesco T "Angine de poitrine guérie par la résection du sympathique cervico thoracique" *Bull d l'Acad d méd d Paris* 1910 LXXXIV 93
- Mandl F "Weitere Erfahrungen mit der paravertebralen Injektion bei der Angina pectoris" *Wien klin Wchnchr* 1915 XXXVIII 759
- Marshall C R and Wigner J H "The Pharmacological Action of Mannitol Pentamtrate" *Brit M J* 1902 II 1231
- Murrell W "Nitro-glycerine as a Remedy for Angina Pectoris" *Lancet* 1879 I 80 113 151 and 225 (This paper reports the introduction of nitroglycerine as a therapeutic measure in angina pectoris)
- O'Shaughnessy L "Surgical Treatment of Cardiac Ischemia" *Lancet* 1937 I 185
- Richardson E P and White P D "Sympathectomy in the Treatment of Angina Pectoris Comparison of Results with Those from Paravertebral Alcohol Injections" *Am J M Sc* 1919 CLXXVII, 161
- Singer R "Die erste operative Behandlung der Angina pectoris durch Ramiscotomia anterior C-D" *Wien klin Wchnchr* 1927 XL, 989
- Stanton E J Schildt, P J and Beck C S "The Effect of Abrasion of the Surface of the Heart upon Inter coronary Communications" *Am Heart J* 1941 XXII, 529

- Swetlow G I "Paravertebral Alcohol Block in Cardiac Pain" *Am Heart J* 1946 I 393
- White J C and White P D "Angina Pectoris Treatment with Paravertebral Alcohol Injections" *JAMA* 1928 XC 1099

### Recent References (1944-1950)

- Anrep G V Barsoum G S Kenawy M R and Misrahy G "Therapeutic Uses of Khellin Method of Standardization" *Lancet* 1947 I 557
- Anrep G V Kenawy M R and Barsoum G S "The Coronary Vasodilator Action of Khellin" *Am Heart J* 1949 XXXVII 531
- Armbrust C A Jr and Levine S A "The Treatment of Angina Pectoris with a Preparation of Khellin (Ammi Visnaga)" *Am J M Sc* 1950 CCXX 127
- Arnulf G "La résection du plexus préaortique dans l'angine de poitrine" *Arch d mal d coeur* 1949 XLII 1191
- Beck C S "Revascularization of the Heart" *Surgery* 1949 XXVI 82
- "Propylthiouracil in the Treatment of Angina Pectoris. A Comparison with Thiouracil Therapy" *Ann Int Med* 1950 XXXII 528
- Beck C S Stanton E Batuchok W and Lester E "Revascularization of Heart by Graft of Systemic Artery into Coronary Sinus" *JAMA* 1948 CXVXVII 436
- Ben Asher S "Further Observations on the Treatment of the Anginal Syndrome with Thiouracil" *Am Heart J* 1947 XXXIII 490
- "Propylthiouracil in the Treatment of Angina Pectoris. A Comparison with Thiouracil Therapy" *Ann Int Med* 1950 XXXII 528
- Blumgart H L Freedberg A S and Buka R "Treatment of Euthyroid Cardiac Patients by Producing Myxedema with Radioactive Iodine" *Proc Soc Exper Biol & Med* 1948 LXVII 190
- Blumgart H L Freedberg A S and Kurland G S "Hypothyroidism Produced by Radioactive Iodine (I 131) in the Treatment of Euthyroid Patients with Angina Pectoris and Congestive Heart Failure. Early Results in Various Types of Cardiovascular Diseases and Associated Pathologic States" *Circulation* 1950 I 1105
- DiPalma J R and Magovern J J "Disadvantages of Thiouracil Treatment of Angina Pectoris" *Am Heart J* 1946 XXXII 494
- Eisen M E and Gross H "Vitamin E in Arteriosclerotic Heart and Peripheral Vascular Disease" *New York State J Med* 1949 XLIX 2422
- Evans J A Poppen J L and Tobias J B "Relief of Angina Pectoris by Sympathectomy. Report of Results in Ten Patients Subjected to High Thoracolumbar Sympathectomy Including the Anginal Pathway" *JAMA* 1950 CXLIV 1432
- Fauteux M "Pericoronary Neurectomy Associated with Ligation of Great Coronary Vein in Treatment of Some Forms of Coronary Disease" *Union Medicale du Canada* 1945 LXXIV 424
- Fauteux M and Swenson O "Pericoronary Neurectomy in Abolishing Angina Pain in Coronary Disease. An Experimental Evaluation" *Arch Surg* 1946 LIII 169
- Greiner T Gold H Cattel McK and others "Method for Evaluation of Effects of Drugs on Cardiac Pain in Patients with Angina of Effort. Study of Khellin (Visamin)" *Am J Med* 1950 IX 143
- Herrmann G R "Experimental and Clinical Studies in Hypercholesterolemia and Atherosclerosis and the Effect of Decholesterolizing Agents" *Am Heart J* 1947 XXXIII 711
- Hildreth E A et al "An Experimental Study of Practical Diets to Reduce the Human Serum Cholesterol" *J Clin Investigation* 1951 XXX 649
- Horlick L Katz L N and Stamler J "The Effect of a Low Fat Diet on the Spontaneously Occurring Arteriosclerosis of the Chicken" *Am Heart J* 1949 XXXVII 689
- Levine E B and Sellers A L "Testosterone in Angina Pectoris" *Am J M Sc* 1946 CCXII 7
- Lian C Siguer F Leveau and Crosnier "Les infiltrations novocainiques et la résection chirurgicale du plexus nerveux préaortique dans le traitement de l'angine de poitrine" *Arch d mal d coeur* 1949 XLII 215
- McAllister F F Leightinger D and Beck C S "Revascularization of Heart by Vein Graft from Aorta to Coronary Sinus" *Ann Surg* 1951 CXXXIII 153

- Morrison L M and Gonzales W F "Results of Treatment of Coronary Arteriosclerosis with Choline" *Am Heart J* 1950 XXXIX 729
- Policzer M "On the Value of Methylthiouracil in the Treatment of Cardiac Disease Report on 42 Cases" *Cardiologia* 1948 XIII 290
- Ravdin, I S and Katz, K H "Vitamin E in the Treatment of Angina Pectoris" *New England J Med* 1949 CCXL 331
- Rinzler E H Bakst H Benjamin Z H Bobb A L and Travell J "Failure of Alpha Tocopherol to Influence Chest Pain in Patients with Heart Disease" *Circulation* 1950 I 288
- Russek H I Naegele C F and Regan F D "Alcohol in the Treatment of Angina Pectoris" *J.A.M.A.* 1950 CXLIII 355
- Russek H I Regan F D and Naegele C F "One Hundred Per Cent Oxygen in the Treatment of Acute Myocardial Infarction and Severe Angina Pectoris" *J.A.M.A.* 1950 CXLIV 373
- Scott R C Iglaue A Green R S Kaufman J W Berman B and McGuire J "Studies on the Effect of Oral and Parenteral Administration of Vitamin (Khellin) in Patients with Angina Pectoris" *Circulation* 1951 III III
- Simon A J Dolgin M Solway A J L Hirschmann J and Katz, L N A Re evaluation of Papaverine in the Treatment of Angina Pectoris" *J Lab & Clin Med* 1949 XXXIV 992
- Steiner A "Effect of Choline in the Prevention of Experimental Aortic Atherosclerosis" *Arch Path* 1948 XLV 347
- Steiner A Bevans M and Kendall F E "Production of Arteriosclerosis in Dogs with Cholesterol and Thiouracil" *Federation Proc Fed Am Soc of Exper Biol* 1948 VII 280
- White J C and Bland, H F "The Surgical Relief of Severe Angina Pectoris Methods Employed and End Results in 83 Patients" *Medicine* 1948 XXVII 1

#### Acute Coronary Occlusion and Myocardial Infarction

- Barnes A R and Ball R. G "The Incidence and Situation of Myocardial Infarction in One Thousand Consecutive Postmortem Examinations" *Am J M Sc* 1932, CLXXXIII 215
- Bartels E C and Smith H L "Gross Cardiac Hypertrophy in Myocardial Infarction" *Am J M Sc* 1932 CLXXXIV 452
- Bland E F and White H H "Coronary Thrombosis (with Myocardial Infarction) Ten Years Later" *J.A.M.A.* 1941 CXVII 1171
- Blumgart H L "Multiple Fresh Coronary Occlusions in Patients with Antecedent Shock" *Arch Int Med* 1941 LXVIII 181
- Blumgart H L Schlesinger M J and associates "Experimental Studies on the Effect of Temporary Occlusion of Coronary Arteries" *Tr A Am Physicians* 1937 LII 210 and *Am Heart J* 1941 XXII 374
- "Studies on the Relation of the Clinical Manifestations of Angina Pectoris Coronary Thrombosis and Myocardial Infarction to the Pathologic Findings" *Am Heart J* 1940 XIX 1
- Burch G E and Voorhes N W "Studies of Incidence of Coronary Occlusion and Angina Pectoris in White and Negro Races" *Am J M Sc* 1939 CXCVIII 685
- Coelho E *L'infarctus du myocarde Etude experimentale electrocardiographique et clinique* Masson et Cie Paris 1934
- Cushing E H et al "Infarction of the Cardiac Auricles (Atria)" *Brit Heart J* 1942, IV 17
- Davis N S., III "Coronary Thrombosis Without Pain Its Incidence and Pathology" *J.A.M.A.* 1932, XCVIII 1806
- Drake E H "Long Survival Following Coronary Thrombosis" *Am Heart J* 1940 XX, 634
- Feil H "Preliminary Pain in Coronary Thrombosis" *Am J M Sc* 1937 CXCVIII 42
- Garvin C F., and Work, J L "Coronary Embolism Report of Three Cases" *Am Heart J* 1939 XVIII 747
- Gorham L W and Martin E J "Coronary Occlusion With and Without Pain Analysis of 100 Cases in Which Autopsy Was Done" *Arch Int Med* 1938 LXII 821

- Hamman L Spontaneous Mediastinal Emphysema of the Lungs *Tr A Am Phys*  
*cians* 1937 LII 311 and *Bull Johns Hopkins Hosp* 1939 LXIV 1
- Hammer A Ein Fall von thrombotischem Verschlusse einer der Kranzarterien des  
 Herzens *Wien med Wchnschr* 1878 XXVIII 97
- Herrick J B Clinical Features of Sudden Obstruction of the Coronary Arteries  
*JAMA* 1912 LIX 2015
- "On Mistaking Other Diseases for Coronary Thrombosis *J M Soc New Jersey*  
 1935 XXXII 590
- Horne E F and Weiss M M Coronary Thrombosis and Its Effect on Size of  
 Heart *Am J M Sc* 1935 CLXXXIX 859
- Jacobi M Keuler M and Silverman I "Paradoxical Embolism of the Coronary  
 Artery *Am Heart J* 1934 IX 414
- Jamison S C and Hauser G H "Angina Pectoris in a Youth of Eighteen" *JAMA*  
 1925 LXXV 1398
- Langendorf R "Electrocardiogram in Auricular Infarction *Acta med Scandinav* 1939  
 C 136
- Leary T and Wearn J T Two Cases of Complete Occlusion of Both Coronary  
 Orifices *Am Heart J* 1930 V 412
- Leonard B W and Daniels W B Perforation of the Interventricular Septum Caused  
 by Coronary Occlusion *Am Heart J* 1938 XVI 751
- Levine S A Coronary Thrombosis Its Various Clinical Features *Medicine* 1919  
 VIII 245
- Levine S A and Tranter C L Infarction of the Heart Simulating Acute Surgical  
 Abdominal Conditions *Am J M Sc* 1918 CLV 57
- Levy R L *Diseases of the Coronary Arteries and Cardiac Pain* Macmillan Co New  
 York 1936
- Lisa J R and Ring A Myocardial Infarction or Gross Fibrosis Analysis of One  
 Hundred Necropsies" *Arch Int Med* 1932 L 111
- Mallory G A White P D and Salcedo-Salgar J The Speed of Healing of Myo-  
 cardial Infarction *Am Heart J* 1939 XVIII 647
- Marie ■ *L'infarctus du myocarde et ses conséquences ruptures plaques fibreuses*  
*aneurismes du coeur* Thesis No 88 G Carré et C Naud Paris 1896
- Master A M Dack S and Jaffe H L "The Basal Metabolic Rate in a Patient with  
 Coronary Artery Thrombosis When Placed on an 800 Calorie Diet *J Mt Sinai Hosp*  
 1935 I 263
- "Postoperative Coronary Artery Occlusion *JAMA* 1938 CX 1415
- Meakins J C and Eakin W W "Coronary Thrombosis A Clinical and Pathological  
 Study *Canad M A J* 1932 XXVI 18
- Moragues V "Spontaneous Rupture of a Papillary Muscle of the Heart Report of a  
 Case" *Am Heart J* 1939 XVII 106
- Obrastzow W P and Straschesko N D "Zur Kenntnis der Thrombose der Kor-  
 onararterien des Herzens *Ztschr f klin Med* 1910 LXXI 116
- Pardee H E B "An Electrocardiographic Sign of Coronary Artery Obstruction  
*Arch Int Med* 1920 XXVI 244
- Parkinson J and Bedford D E "Successive Changes in the Electrocardiogram after  
 Cardiac Infarction (Coronary Thrombosis) *Heart* 1928 XIV 195
- Paterson J C "Vascularization and Hemorrhage of Intima of Arteriosclerotic Coronary  
 Arteries *Arch Path* 1936 XXXII 313
- "Some Factors in Causation of Intimal Hemorrhages and in Precipitation of  
 Coronary Thrombi *Canad M A J* 1941 XLIV 114
- Porter W T "On the Results of Ligation of the Coronary Arteries *J Physiol* 1894  
 XV 121 and *J Exper Med* 1896 I 46
- Ruchelli A P and Marra A J "Infarto del Miocardio en jóvenes de veinte (20)  
 años *Semana Méd* 1943 L 314
- Saphir O "Coronary Embolism" *Am Heart J* 1933 VIII 312
- Saphir O Priest W S Hamburger W W and Katz L N "Coronary Arteriosclerosis,  
 Coronary Thrombosis and the Resulting Myocardial Changes An Evaluation of  
 Their Respective Clinical Pictures Including the Electrocardiographic Records Based  
 on the Anatomical Findings *Am Heart J* 1935 X 762
- Schaps L "Ein Fall von spontaner Herzruptur bei einem Säugling" *Arch f Kinderheilk*  
 1905 XL, 126

- Schlesinger M J "An Injection Plus Dissection Study of Coronary Artery Occlusions and Anatomoses" *Am Heart J* 1938 XV, 528
- Scott P W and Garvin C F "Myocardial Infarction with Rupture of the Septum" *Am Heart J* 1939 XVII 375
- Smith F M "The Ligation of Coronary Arteries with Electrocardiographic Study" *Arch Int Med* 1918 XLII 8
- Smith F M "Electrocardiographic Changes Following Occlusion of the Left Coronary Artery" *Arch Int Med* 1923 XXXII 497
- Sprague H H and Organ E S "Electrocardiographic Study of Cases of Coronary Occlusion Proved at Autopsy at the Massachusetts General Hospital 1914-1934" *New England J Med* 1935 CCXII 903
- Sutton, H C and Davis M B "Effects of Exercise on Experimental Cardiac Infarction" *Arch Int Med* 1931 XLVIII 1118
- Whitten M B "Localization of Myocardial Infarction" *Texas State J Med* 1931 XXVII 291
- Wilson F N and associates "The Electrocardiogram in Myocardial Infarction with Particular Reference to the Initial Deflections of the Ventricular Complex" *Heart* 1933 XVI 143
- Wood F C and Wolferth C C "An Electrocardiographic Study of Coronary Occlusion. The Inadequacy of the Three Conventional Leads in Recording Certain Characteristic Changes in Action Currents" *J Clin Investigation* 1932 XI 815

#### Recent References (1944-1950)

- Benhumol A B, Schlesinger P and Cotrim M R "The Use of Multiple Esophageal Leads in Localizing and Evaluating Extension of Posterior Myocardial Infarctions" *Cardiologia* 1950 XVI 37
- Blumgart H L "Effort and Acute Myocardial Infarction" *JAMA* 1945 CXXVIII 775
- Brink A J "The Coronary Vessels in the Bantu. A Preliminary Report on the Coronary Artery Pattern in the Adult Bantu" *Clin Proc Cape Town* 1949 VIII 137
- Chambers W N "Blood Pressure Studies in 100 Cases of Coronary Occlusion with Myocardial Infarction" *Am J Med Sc* 1947 CCXIII 40
- Chen Lang Tung "Coronary Thrombosis Among the Chinese" *Chinese Med J* 1948 LXVI 587
- Cleland J B "Cardiac Infarction and Coronary Disease in General in Post Mortem Examinations" *M J Australia* 1949 II 733
- Dack S, Paley H and Sussman M L "A Comparison of Electrokymography and Roentgenkymography in the Study of Myocardial Infarction" *Circulation* 1950 I 451
- de Azevedo Ponde Adrian and de Azevedo Ponde Albert "Do emprego de derivações torácicas suplementares para o diagnóstico do enfarte do miocárdio" *Arg brasil d cardiol* 1950 III 1
- Diaz Rivera R S and Miller A J "Rupture of the Heart Following Acute Myocardial Infarction" *Am Heart J* 1948 XXXV 126
- Dressler W and Roesler H "High T Waves in the Earliest Stage of Myocardial Infarction" *Am Heart J* 1947 XXXIV 627
- Evans W F and Graybiel A "Death Following Coronary Thrombosis in a Young Woman Nineteen Years of Age" *Am Heart J* 1948 XXXV 485
- Freedberg A S, Blumgart H L, Zoll P M and Schlesinger M J "Coronary Failure. The Clinical Syndrome of Cardiac Pain Intermediate Between Angina Pectoris and Acute Myocardial Failure" *JAMA* 1948 CXXXVIII 107
- Friedman S and White P D "Rupture of the Heart in Myocardial Infarction. Experience in a Large General Hospital" *Ann Int Med* 1944 XXI 778
- Furman R H and Meneely G R "Acquired Defect of the Septum Interventriculorum as a Special Form of Myocardial Rupture Complicating Coronary Artery Disease with Myocardial Infarction" *Am J Med* 1948 V 313
- Gardner F E and White P B "Coronary Occlusion and Myocardial Infarction Associated with Chronic Rheumatic Heart Disease" *Ann Int Med* 1949 XXXI 1003
- Hunter W S "Coronary Occlusion in Negroes" *JAMA* 1946 CXXXI 12
- Jetter W W and White P D "Rupture of the Heart in Patients in Mental Institutions" *Ann Int Med* 1944 XXI 783



- MacDougall W G "Fatal Coronary Occlusion in Girl Aged 16" *Lancet* 1949 II 741
- Myers G B "QRS T Patterns in Multiple Precordial Leads That May Be Mistaken for Myocardial Infarction I Left Ventricular Hypertrophy and Dilatation" *Circulation* 1950 I 844
- II "Right Ventricular Hypertrophy and Dilatation" *Ibid* 1950 I 860
- Myers G B Klein H A and Hiratzka T II "Correlation of Electrocardiographic and Pathologic Findings in Anteroseptal Infarction" *Am Heart J* 1948 XXXVI 535
- Myers G B Klein H A and Hiratzka T II "Correlation of Electrocardiographic and Pathologic Findings in Large Anterolateral Infarcts" *Am Heart J* 1948 XXXVI 838
- "IV Correlation of Electrocardiographic and Pathologic Findings in Infarction of the Interventricular Septum and Right Ventricle" *Ibid* 1949 XXXVII 720
- "VI Correlation of Electrocardiographic and Pathologic Findings in Posterolateral Infarction" *Ibid* 1949 XXXVIII 837
- Newman M "Coronary Occlusion in Young Adults: Review of Fifty Cases in the Services" *Lancet* 1946 II 409
- Pickard C M Owen J G and Dammin G J "Aneurysms of Coronary Arteries Due to Polyarteritis Nodosa Occurring in Infant: Report of Case with Coronary Artery Thrombosis and Myocardial Infarction" *J Lab & Clin Med* 1947 XXVII 1513
- Rabinovich N P "O prinzhiznennoi diagnostike razryva nezhdzheludochkovo per gorodki na pochyve infarkta miokarda" *Alin Med* (Moscow) 1947 XXV 61
- Roesler H and Dressler W "An Electrocardiographic Pattern of Infarction of the Interventricular Septum Extending from the Anterior to the Posterior Aspect of the Heart" *Am Heart J* 1947 XXXIV 817
- Shivelhood E K "Myocardial Infarction in a Twelve Year Old Boy with Diabetes" *Am Heart J* 1948 XXXV 655
- Smith F J Keyes J W and Denham R M "Myocardial Infarction: A Study of the Acute Phase" *Tr Am Clin and Climat A* 1940 LXII
- Soderstrom N "Myocardial Infarction and Mural Thrombosis in the Atria of the Heart" *Acta med Scandinav* 1948 CXXXII Suppl 217
- Ungar H and Ullman T D "Acquired Defect of the Interventricular Septum of the Heart" *Cardiologia* 1950 XVI 67
- Wang C H Bland E F and White P D "A Note on Coronary Occlusion and Myocardial Infarction Found Postmortem at the Massachusetts General Hospital During the Twenty Year Period from 1926 to 1946 Inclusive" *Ann Int Med* 1948 XXIX, 601
- Warner H R "Painless Myocardial Infarction" *Minnesota Med* 1951 XXXIV 49

## Treatment

- Barnum D R Garr W R Gilbert N C and Fenn G K "Coronary Thrombosis Treated with Xanthines: Experience from the Standpoint of Mortality and Incidence of Thromboembolic Complications" *Quart Bull Northwestern Univ Med School* 1950 XXIV 5
- Blumgart H L Freedberg A S Zoll P M Lewis H L and Wessler S "The Effect of Dexamorol on the Heart in Experimental Acute Coronary Occlusion" *Tr A Am Physicians* 1947 LX 227
- Borg J "Observations on the Occurrence and Prevention of Sudden Death" *Tr 4th Therap Soc* 1939 XXXIX, 115
- Burke G E, and Wright, I S "Tromexan—3,3 Carboxymethylenebis (4 Hydroxy coumarin) Ethyl Ester: Experimental and Clinical Properties" *Circulation* 1951 III 164
- Doles H McG "Further Observations of Prothrombin Determinations and Vitamin K Therapy in Acute Coronary Occlusions" *Southern M J* 1947 XL 965
- Fauteux M "Resultats obtenus par la denervation des arteres coronaires associee ou non a la ligature de la grande veine coronarie dans le traitement de la maladie coronarienne" *Mem Acad Chir* 1948 LXXIV 528
- Goldstein E and Wolff L "Hemorrhagic Pericarditis in Acute Myocardial Infarction Treated with Bishydroxycoumarin" *JAMA* 1951 CXLVI 616

- Holten C. "Anticoagulants in the Treatment of Coronary Occlusion" *Ugeskr f Laeger* 1950 CXII 1405
- Irvin C W and Burgess A M "The Abuse of Bed Rest in the Treatment of Myocardial Infarction" *New England J Med* 1950 CCXLIII, 486
- James D F Butler J J Bennett I L Jr and Scheinberg E "Studies on Dicumarol in Human Beings Its Neutralization by Vitamin K Oxide Menadione Bisulfite Synkayvite and Blood" *J Clin Investigation* 1948 XXVII 541
- Johns T N P Sanford M C and Blalock A "An Experimental Study of the Anastomosis of Arteries in the Coronary Sinus of the Heart of the Dog" *Bull Johns Hopkins Hosp* 1950 LXXXVII 1
- Levine S A., and Lown B "The Arm Chair Treatment of Acute Coronary Thrombosis" *J.A.M.A* 1951 in press
- Nichol E S and Borg J F "Long Term Dicumarol Therapy to Prevent Recurrent Coronary Artery Thrombosis" *Circulation* 1950 I 1097
- Sampson J J and Singer I M "Plasma and Blood Infusion Following Myocardial Infarction" *Am Heart J* 1949 XXXVIII 54
- Wright I S Marple C E and Beck D F "Report of the Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis with Myocardial Infarction" *Am Heart J* 1948 XXXVI 801

# NEUROCIRCULATORY ASTHENIA (DA COSTA'S SYNDROME, ALSO CALLED "THE SOLDIER'S HEART," "EFFORT SYNDROME," AND ANXIETY NEUROSIS) CARDIAC NEUROSIS AND PSYCHOSIS

---

## NEUROCIRCULATORY ASTHENIA

**Introduction** Despite considerable research on this mysterious malady since the last edition of this book and the elucidation of certain of its aspects the fundamental mechanism still eludes us and we have as yet no specific therapy. The chapter therefore requires relatively slight changes.

Neurocirculatory asthenia also called less adequately the soldier's heart, effort syndrome and the anxiety neurosis is an important condition of instability and abnormal irritability of the nervous and circulatory systems of unknown cause. It tends to be precipitated as an acute disorder in many persons by physical exhaustion, nervous strain and infections and so constitutes a kind of fatigue syndrome, in some individuals however who appear to be constitutionally inadequate. It is a more or less chronic condition, usually associated with or a part of, a psychoneurosis of the anxiety type. It is not in itself a disease of either heart or nervous system but a functional circulatory and nervous disorder often confused or associated with heart disease hence it forms an essential part of this book.

In the present state of our knowledge, and until the problem is solved I would suggest the following definition: *Neurocirculatory asthenia is a condition of ill health characterized by a group of symptoms consisting of dyspnea (often with sighing respiration), palpitation, exhaustion, precordial pain (most often an ache), dizziness, nervousness and sometimes tremor, sweating, headache and syncope, aggravated by effort or excitement and attending or following anxiety neuroses, infections or physical or nervous strains especially in hypersensitive individuals who in extreme cases may show the condition more or less constantly with little or no provocation.* That such a

state of ill health exists there can be no doubt no matter what its pathogenesis or exciting factors. Until we can give it a fundamentally better designation the descriptive term neurocirculatory asthenia seems still to be the best. It is neither fatigue per se nor infection nor thyrotoxicosis nor nervous strain nor psychoneurosis it is a state of ill health which may attend or follow any of these conditions or indeed others too or even frequently stand alone.

Physical effort of extreme degree will always produce symptoms of circulatory distress but fatigue of skeletal muscles or of nervous system may prevent such effort. The symptoms of circulatory distress are dyspnea palpitation and precordial or substernal oppression alone or combined. Generally associated with them are weakness and often dizziness faintness and tremor. The combination of these symptoms occasioned by exertion has been called the effort syndrome. Such effort syndrome may be induced easily in weak tired sick or nervous persons and with difficulty in strong well trained and calm individuals whether heart disease is present or not. Even a perfectly normal person if sufficiently strenuous will show the syndrome in some form perhaps having dyspnea alone palpitation substernal or precordial oppression or two or three of these symptoms together. It is likely that under such circumstances in *normal* persons the relative abilities of the myocardium to maintain the general circulation and of the coronary circulation to maintain the myocardium determine whether dyspnea or pain will be the predominant symptom in most normal persons dyspnea will be preponderant but even in normal persons a third factor besides myocardial and coronary reserves namely nervous sensitivity must be taken into account as modifying symptoms or exaggerating one or another especially precordial pain palpitation or faintness. *Hypersensitive* individuals in whom the effort syndrome is easily induced are likely to develop the same symptoms on excitement as on exertion at such times the symptoms form an excitement syndrome and not an effort syndrome.

The effort syndrome though easily induced might be considered at first thought to be unworthy of any special discussion since so far as we know it is not an organic disease and since it may occur in perfectly normal persons but when it is of high degree that is when it is very easily induced and the symptoms are marked it is important for three reasons. In the first place it is itself often a partially or completely incapacitating condition. Secondly proper treatment is very important and is often neglected. And thirdly it is essential to distinguish it from organic heart disease or to recognize its presence when it complicates organic heart disease.

An abnormally high degree of effort syndrome has long been recognized generally as but a part of a neurasthenic state and it has so been labeled in medical practice. Occurring with great frequency among the British soldiers in India and among the Union soldiers during the American Civil War as the result of excessive strain and hardship it was called the excitable or irritable heart of soldiers (Myers 1870 DaCosta 1871). DaCosta's classical account is the first good description of the condition and so deserves quotation here.

DaCosta J M On Irritable Heart a Clinical Study of a Functional Cardiac Disorder and Its Consequences *Am J M Sc* 1871 LXI 17

'In this paper I propose to consider a form of cardiac malady common among soldiers but the study of which is equally interesting to the civil practitioner on account of its intimate bearing on some obscure or doubtful points of pathology Much of what I am about to say I could duplicate from the experience of private practice yet I prefer to let this inquiry remain as it was originally conducted on soldiers during our late war The observations here collected were made on a series of upwards of three hundred cases

**GENERAL CLINICAL HISTORY**—The general clinical history of many of the cases was this —

"A man who had been for some months or longer in active service would be seized with diarrhoea annoying yet not severe enough to keep him out of the field or attacked with diarrhoea or fever he rejoined after a short stay in hospital his command and again underwent the exertions of a soldier's life He soon noticed that he could not bear them as formerly he got out of breath could not keep up with his comrades was annoyed with dizziness and palpitation and with pain in the chest his accoutrements oppressed him and all this though he appeared well and healthy Seeking advice from the surgeon of the regiment, it was decided that he was unfit for duty and he was sent to a hospital where his persistently quick acting heart confirmed his story though he looked like a man in sound condition Any digestive disturbance which might have existed gradually passed away but the irritability of the heart remained and only very slowly did the excited organ return to its natural condition Or it failed to do so notwithstanding the use of remedies which control the circulation thus the case might go on for a long time and the patient after having been the round of hospitals would be discharged or as unfit for active duty placed in the Invalid Corps

**CAUSES**—In discussing the causes we are led to examine some of the most interesting questions connected with this inquiry But in no part of it is it more difficult to arrive at fixed conclusions for many causes seem at times to have combined and it is scarcely possible even by the most rigorous analysis to fix specially upon one In the subjoined table great care has been exercised to arrive at the probable causing element The cases which have served as its basis have been only so far selected that doubtful or ill marked ones have been excluded and that those patients who were chosen were for the most part in good general health

*Analysis of 200 Cases*

Fevers	34	17 per cent
Diarrhoea	61	30.5 per cent
Hard field service particularly excessive marching	69	34.5 per cent
Wounds injuries rheumatism scurvy ordinary duties of soldier life and doubtful causes	36	18 per cent
	<hr/> 200	<hr/> 100

But in looking further and in endeavouring to explain the nature of the malady there is room for much doubt and difference of opinion

**TREATMENT** The treatment is never a short one and the question arises, would it not be better for the government at once to discharge these heart cases? I think not The very worst ones those which after some months of treatment show

no decided improvement had better be discharged      Until I understood the malady I retained the patients a long period in the hospital later in the war a short time sufficed to make the proper disposition of them

"      And from a military point of view further it enforces the lessons how important it is not to send back soldiers just convalescent from fevers or other acute maladies too soon to active work      that recruits especially very young ones be as far as practicable exercised and trained in marches and accustomed to fatigue before they are called upon to undergo the wear and tear of actual warfare and it exhibits some of the dangers incident to the rapid and incessant manœuvring of troops

Rediscovered as a common military disorder in World War I this state of ill health was called the soldier's heart : disordered action of the heart and later effort syndrome The term neurocirculatory asthenia was finally employed in this country (Oppenheimer and associates 1918) and this remains at the present time the most satisfactory designation because it expresses its abnormal character by referring to both neurasthenic state and circulatory symptoms and at the same time it does not limit the term to effort or irritability or soldier or make it too general by calling it by the vague inclusive designation cardiac neurosis : It is simply one type of cardiac neurosis or of irritability of the heart it occurs in civilians as well as in soldiers it results from excitement as well as from effort and it is not a normal response to ordinary effort Also its symptoms are not exactly like those produced by effort in a normal healthy person

Frequency It is impossible to state accurately the frequency of neurocirculatory asthenia for several reasons The borderline is very wide and indistinct and where the normal response ends and the abnormal response begins especially with such variable factors as human individuals it is impossible to say Moreover a normal person may have the condition for a short time during or after an acute illness or especial fatigue without its being particularly noted by patient or doctor And finally it has been included by most practicing physicians as a part of the more general terms : neurasthenia nervous prostration and neurosis

It is possible however to estimate roughly its frequency when well marked Although common enough in civilian life it is far less frequent and less severe than in the army in wartime Lewis (1940) stated that during World War I sickness imputed by medical officers of the British Army to disturbances of the cardiovascular system was a chief malady one such case being numbered for every four cases of wound following chest complaints as the second largest group of medical ailments Five out of six of those cardiac cases suffered from neurocirculatory asthenia After the World War of 1914-1918 there were 44 000 British soldiers who were pensioned for neurocirculatory asthenia In World War II the condition cropped up in prominent degree in only the most strenuous campaigns but in mild form it was encountered in many psychoneurotic soldiers undergoing their training in camps at home

Of a series of 3 000 civilian patients with cardiac symptoms or signs who sought medical advice both in hospital and in private practice in New England (White and Jones, 1928) 302 or 10 per cent were found to have neurocirculatory asthenia alone and 62 or 2 per cent more showed well marked neurocirculatory asthenia complicating organic heart disease over half of such disease being of rheumatic type and another quarter of hypertensive type. Nearly 3 per cent of 2 314 cases of organic heart disease showed definite neurocirculatory asthenia. A more recent analysis of 5,000 private patients with cardiac symptoms or signs seen by myself has revealed 687 (13·7 per cent) with definite neurocirculatory asthenia. 448 (65·2 per cent) of these were uncomplicated by organic heart disease. 135 (19·8 per cent) were so complicated and in the remainder (104 or 15·2 per cent) there was doubt about the presence of organic heart disease. Among the cases of organic heart disease found with neurocirculatory asthenia (a total of 47 per cent of the organic heart cases) rheumatic heart disease was most frequent (44·4 per cent), coronary heart disease was second (21·4 per cent) and hypertensive heart disease was third (18 per cent), there was only one case of cardiovascular syphilis.

The victims of the disorder are physically unfit as it were chronically out of condition, unable to maintain any degree of physical effort and quickly accumulating respiratory inefficiency and an excess of lactic acid on exercise.

**Etiology Cause** The cause of neurocirculatory asthenia is not known. The symptoms suggest that it may be a disorder of the autonomic or vegetative nervous system, a true neurosis not necessarily a psychoneurosis but, even if it is, we are as yet unaware of its pathogenesis. The fundamental origin of the irritability and fatigability of the nervous system in so-called neurasthenia is still obscure; these have usually been called functional disorders but the mechanism of such disorders is as yet unexplained. Abnormalities of central nerve cells induced by fatigue in experimental animals have been noted and may be possible factors. Moreover, why gastrointestinal symptoms are most prominent in some neurasthenic patients, cerebral symptoms in others and cardiovascular (neurocirculatory asthenia) in others has not been explained. Variations in innervation or early accidental association with other troubles (indigestion, headache, extrasystoles or cardiovascular symptoms on exertion) may be the answer. We can only say now that in some patients neurasthenia manifests itself preponderantly by circulatory symptoms and that neurasthenia itself is a disorder commonly found in certain individuals usually under especial strain who are equipped with a particularly sensitive nervous system.

**Age** Neurocirculatory asthenia is commonest in young adults but it may occur at any age after early childhood; it appears to be very rare in young children and it tends to decrease in incidence after early adult life. Of the 365 cases of this condition in White and Jones' series over half were between twenty and forty years old, 23·9 per cent being in the third and 27·4 per cent in the fourth decade of life. In the second decade 7·4 per cent were found.

After the age of fifty years there were still a moderate number of cases—15.3 per cent. In war time among the soldiers the great majority of cases were found in the third and fourth decades doubtless because such age groups made up the bulk of the soldiers.

**Sex** Females are affected more often than males. The ratio in the series of White and Jones was 59 per cent female to 41 per cent male.

**Heredity** One of the most fundamental etiologic factors is that of heredity. It is common to find that the close relatives and recent ancestors of patients with neurocirculatory asthenia have also had sensitive nervous systems having suffered perhaps from this very same condition in the course of nervous prostration or other such trouble. Recent studies have suggested that neurocirculatory asthenia belongs to the Mendelian dominant group of inherited disorders (Wheeler et al. 1948).

**Strain** Besides heredity the one other etiologic factor of greatest importance is that of strain. This may be the result of worry over business, social or family troubles, emotional conflicts, physical or nervous fatigue or both (as in the war), insomnia, exhaustion from acute infection or other illness or undernourishment.

The toxic effect of tobacco, alcohol, tea, coffee and other substances does not itself cause neurocirculatory asthenia, although it may aggravate or perhaps even precipitate it. During World War I (1914–1918) it was thought that overindulgence in these things, particularly in tobacco and alcohol, might explain the great frequency of neurocirculatory asthenia, but actually the reverse was found, namely that the victims of this disorder, realizing their sensitiveness, indulged in these things less than did the average soldier for otherwise their symptoms were often aggravated.

Other possible fundamental causes of neurocirculatory asthenia that have been suggested during the past 25 years are thyrotoxicosis, low grade active infection, adrenal hyperactivity, hyperventilation resulting in alkalosis and salt lack, but none of these possible factors have been confirmed. All these conditions may precipitate or aggravate the symptoms of neurocirculatory asthenia, but they do not seem to be the fundamental cause. Hyperventilation combined with an anxiety neurosis is the nearest approach to the answer to date, the neurosis causing in some unknown way a sighing respiration with hyperventilation, the latter inducing in its turn faintness, dizziness, palpitation and precordial discomfort.

**Pathology** There are no known pathologic changes in neurocirculatory asthenia. The heart as a rule is structurally normal, although there is sometimes associated organic disease. No lesions of the nerves or of the glands of internal secretion have been found.

**Symptoms** The symptoms of neurocirculatory asthenia are usually like those of effort syndrome in normal persons. In cases with lesser degrees of neurocirculatory asthenia the symptoms are not only relatively mild but they are fewer in number and in only the pronounced cases are all the classical symptoms present—dyspnea, palpitation, precordial pain and tenderness.



faintness dizziness tremor, sweating and nervousness. In a series of 100 cases of neurocirculatory asthenia the four cardinal symptoms namely palpitation respiratory discomfort precordial pains or aches and exhaustion were of almost the same frequency varying in the order named from 78 to 73 per cent (Craig and White 1934).

The dyspnea is mostly subjective there being an unpleasant consciousness of the ordinary respiratory act without much of any evident labor distress or rapidity of respiration (a breathing trouble often in spells) sometimes there is a tachypnea and during World War I cases were noted with an extreme but temporary acceleration of respiratory rate even to 100 or more per minute. *An interesting and commonly associated phenomenon is the abnormal increase of a tendency to sigh.* In fact the presence of abnormally frequent sighing is a helpful sign of the existence of neurocirculatory asthenia as differentiated from organic heart disease for heart disease even in the presence of heart failure is rarely attended by sighing unless it is complicated by neurocirculatory asthenia.

The palpitation is for the most part simply the keen consciousness of the forceful action of the heart beating regularly and often rather rapidly. arrhythmia is uncommon but if premature beats or paroxysms of tachycardia do appear they usually aggravate the condition considerably and sometimes they set it off.

The precordial pain is as a rule a dull or heavy ache in the left breast, lasting for hours and not radiating but occasionally it is interspersed with sharp stabbing sensations. substernal oppression is unusual though neurocirculatory asthenia may and in fact frequently does complicate angina pectoris. When the heartache or infrequently the substernal ache is severe it may radiate to the left arm and then be mistaken for angina pectoris still more easily. Left breast tenderness is distinctive evidence of neurocirculatory asthenia.

The fourth prominent symptom namely a feeling of exhaustion present almost all the time but especially noticeable the first thing in the morning is a striking characteristic in the great majority of cases of neurocirculatory asthenia. Not rarely it is the outstanding symptom. Other common symptoms—dizziness faintness and tremor—are present in varying degrees and indicate the instability of the nervous state and of the vasomotor control.

It is usually the combination of excitement exertion and fatigue that precipitates the maximum degree of symptoms in a susceptible individual and it is this combination in war times that occasions the great exaggeration of the disorder in so many nervous young soldiers. More or less incapacity results from marked neurocirculatory asthenia often more than that resulting from organic heart disease and sometimes even complete disability ensues. It is a real and not an imaginary incapacity even though at first glance it may have appeared imaginary during World War I (1914–1918) when it was sometimes labeled "malingering" and even though in civilian practice it has frequently been diagnosed as mere nervousness.

An important finding in neurocirculatory asthenia of high degree or easily induced as in civilian life or in early milder training for war is the associated psychoneurosis of anxiety type. So common is this that the two conditions have sometimes been confused one for the other or considered to be synonymous the term anxiety neurosis having come to mean for many the same collection of symptoms which identify neurocirculatory asthenia although strictly one can be neurotically anxious about something without dyspnea chest pain or palpitation. Experience has shown however that one condition can occur without the other as well as that either one can excite the other. Nevertheless the close correlation is helpful in the weeding out of the more pronounced cases of neurocirculatory asthenia from the recruits for the armed services by the neuropsychiatrist who is particularly trained to pick out the psychoneurotics and those likely to become such.

**Signs** The signs of neurocirculatory asthenia are general the heart itself giving no evidence of trouble other than a tendency to increased force of action and sometimes increased rate unless of course it happens to be the seat of organic lesions. A worried expression tremor sometimes flushing somewhat quickened respiration and sweating are commonly found in a well marked case. Special methods of examination such as blood pressure studies roentgenology and electrocardiography reveal no particularly characteristic abnormalities in an occasional case however the T waves in Lead 2 of the electrocardiogram may be temporarily flattened or even inverted probably due either to a preponderant sympathetic nerve imbalance or to an unusually vertical position of the heart (so common in this type of individual of asthenic build) or to both these factors (see Chapters 2 and 9). The blood pressure may be a little elevated and variable. Strength and endurance tests and vital capacity usually show a subnormal value and are considerably reduced in marked cases this fact weakens the value of such strength and vital capacity tests in judging the state of the heart itself. An interesting abnormality is an easily induced oxygen debt on exercise with excess accumulation of lactic acid. Another interesting finding is abnormality of shape of the capillary loops at the base of the nail in neurocirculatory asthenia (Cobb et al 1946) somewhat as has been noted in certain neurotic states.

**Course and prognosis** The course of neurocirculatory asthenia is very variable but the prognosis is always good so far as length of life is concerned in fact better than the normal expectation (Wheeler et al 1950). The degree of incapacity depends on several factors chiefly on the intensity of the symptoms and on the adequacy of treatment. Recovery from a considerable degree of neurocirculatory instability is possible with care but the patient is always likely to have a return of trouble if there is a return of the causative factors—infection fatigue worry and emotional stress. If these factors cannot be controlled neither can the neurocirculatory asthenia be controlled. At the height of World War I it was suggested that this condition was but a forerunner of thyrotoxicosis or of heart disease or an accompaniment of infection but none of these prophecies was fulfilled.

Of 558 soldiers with the condition reported by Lewis (1918) during World War I 286 (51 per cent) were found to be unfit for all military service and of the remaining 272, 38 had to be removed from service later. In civilian life complete incapacity is much less for two reasons (1) the degree of neurocirculatory asthenia is as a rule less marked in civilians and (2) the strain of civilian life and work to which the patient must return is less than that of military service. Nevertheless it must be recognized that more or less complete incapacity can occur even in ordinary civilian life. However a follow up study of 173 cases of neurocirculatory asthenia who had been examined by myself for the first time over twenty years ago has shown that the majority are still able to live a useful and reasonably comfortable life (Wheeler Reed Cohen and White, 1950).

A series of 601 war veterans with neurocirculatory asthenia was studied over a period of five years by Grant (1925) to determine the immediate prognosis of the condition. Of these cases 15.3 per cent recovered entirely 17.8 per cent improved 56.2 per cent remained stationary and only 3.2 per cent became worse the remainder became ill or died from other diseases. The incidence of serious disease in the group was 8.7 per cent the most frequent infection was pulmonary tuberculosis (3.7 per cent). The incidence of definite heart disease was only 1 per cent. The total deaths were but 14 (2.3 per cent).

So far as we know there is no tendency for patients with neurocirculatory asthenia either to die prematurely or to develop organic heart disease but they often do live considerably restricted lives.

**Complications** There are no particular complications of neurocirculatory asthenia except the anxiety neurosis although the condition may itself complicate any other trouble such as infection heart disease chronic illness of other nature or trauma. Sometimes the symptoms of neurocirculatory asthenia like other symptoms such as the palpitation resulting from paroxysmal tachycardia lead to anxiety about them and establish an anxiety neurosis and apparently vice versa thus a vicious circle is easily established and is often hard to break.

**Treatment** If fatigue physical or nervous or infectious is primarily or even secondarily responsible for neurocirculatory asthenia rest is the important therapy for the moment and for as long—days weeks or months—as may be necessary adequately to counteract the fatigue. The rest which may need at first to be complete should be followed as soon as possible by a program of rehabilitation re-education and retraining. Reassurance at the start and in adequate doses afterward is often necessary but elaborate psychotherapy is generally not needed. In fact since this condition is neither heart disease nor a mental disorder both cardiologist and psychiatrist are well kept away after the diagnosis has been established so that the patient may not develop unnecessary fears about either heart or mental state unless complications make the presence of such consultants advisable. It is essential at the outset in cases of neurocirculatory asthenia to rule out exciting factors such as infection and important psychoneuroses that in themselves need treatment.

One of the prime essentials in the treatment of neurocirculatory asthenia is to take the patient wholly into one's confidence to explain fully what the situation is so far as we know it and to dispel any fears of heart disease or death. The condition must be discussed seriously not lightly as if it were of no importance. It is just as wrong to regard the whole trouble as negligible or imaginary as it is so often done as it is to regard it as a dangerous or serious state which may threaten life and which demands rest in bed. Equally pernicious are the two extremes of diagnosis (1) myocarditis or cardiac insufficiency and (2) no disease or imaginary trouble. A careless disregard of the disorder with hasty reassurance may make as much of a permanent cripple of the patient who perhaps consults the advice of charlatans for their sympathy after being rebuffed by the regular medical profession as does a grave face with the order to go to bed and to take digitalis. A half hour or an hour spent in full explanation at the onset of trouble or at least at the first medical consultation and a clear outline of treatment may save many days, weeks or even years of invalid existence and hundreds of dollars spent on all kinds of doctors and medicines. So much good can be done in this way that too much emphasis cannot be placed on this method of procedure. It is often more fruitful and may need more skill and understanding than the treatment of a dozen cases of true heart disease.

The plan of life of the patient is to be worked out with care. Usually normal but quiet work and play are to be advised with avoidance of late hours, coffee, tea, overindulgence in alcohol and tobacco, strenuous vacations, excitement in general, too many hours at work and new and burdensome tasks or duties. Often the patient himself is aware of this necessity but he has perhaps disliked to humor his symptoms or to fall behind his fellows in strenuous living in the business, professional and social world. With clear medical advice, however, he realizes the wisdom of doing so and gradually he adjusts himself to suit his symptoms and is surprised at recapturing a feeling of well being. After the preliminary talk a few further visits to the doctor may be all that are necessary to establish a satisfactory cure without the need of a single drug or a visit to some expensive sanitarium. Symptomatic therapy for headache, insomnia or extreme nervousness with bromides or hypnotics may be helpful but should be discontinued as soon as possible to avoid toxic effects and habituation. Digitalis generally makes the condition worse by increasing the force of the heart action or by producing toxic symptoms like anorexia.

Thus rest, reassurance and re-education are the keynotes of the therapy but after the condition is well established and has been wrongly treated for several years it may be very resistant to improvement and some cases fail to respond to even the most enlightened treatment of the day.

Attempts have been made at more or less specific therapy by attacks on certain conditions that have been thought to underlie or at least to accompany neurocirculatory asthenia but these measures have not proved of value or are still in the experimental stage. They include denervation of the adrenal glands, the administration of sodium chloride, various vitamins and other

drugs and intensive psychotherapy We still await a specific cure for routine use

**Differential diagnosis** The three conditions from which neurocirculatory asthenia at first glance may be sometimes difficult to differentiate are true heart disease thyrotoxicosis and psychoneurosis The absence of cardiac enlargement of characteristic murmurs of valvular disease, of hypertension of signs of heart failure of angina pectoris, or of abnormalities of roentgen ray shadow and electrocardiogram indicates at once that heart disease is not responsible for symptoms or incapacity Before the valuable experience of World War I (1914-1918) young adults especially women with uncomplicated neurocirculatory asthenia were occasionally wrongly diagnosed mitral stenosis because of their forceful heart action and of the unfamiliarity of the medical profession with the syndrome of neurocirculatory asthenia, now such errors are rarely made

The absence of exophthalmos of thyroid gland enlargement and of abnormally high basal metabolic rate (carefully measured and judged) rules out thyrotoxicosis

The most difficult differentiation of all is between neurocirculatory asthenia and psychoneurosis particularly of the anxiety type This is true because of the frequency with which one is engrafted upon the other probably much as neurocirculatory asthenia is a common accompaniment of infection though the reverse is not true Since in the easily induced severer grades of neurocirculatory asthenia the anxiety neurosis is almost constantly found there is little or no point in differential diagnosis in this respect in such cases but in other patients more resistant to the condition it may be of considerable importance to distinguish the other exciting factors namely physical exhaustion nervous strain and infection from the anxiety neurosis itself It is probably best until we know more about it to regard neurocirculatory asthenia as a disorder of the autonomic or vegetative nervous system that is as a neurosis in contradistinction to a psychosis or psychoneurosis

The absence of fever or other evidences of infection indicates that neurocirculatory asthenia is not an immediate accompaniment of infection Finally the recent history of nervous strain fatigue or infectious disease in an individual with a sensitive nervous system helps to establish the diagnosis of neurocirculatory asthenia

## PSYCHONEUROSES AND MENTAL DISORDERS

Any psychoneurotic state may have cardiovascular symptoms associated with it or be in part or completely based on a fear or a delusion of heart disease, even with no symptoms whatever This is very different from neurocirculatory asthenia where symptoms may be marked but where there may be no fear or delusion at all In some cases the two conditions may be combined as I have amply noted in the earlier part of this chapter

Heart symptoms or signs should be considered in their true light with relationship to the nervous disorder and specifically treated only if there is congestive failure angina pectoris or some such condition which can be definitely benefited such treatment if indicated may itself result in improvement of the nervous disease and reinforce psychiatric therapy

Mental disorders and nervous instability may be initiated or aggravated by the fatigue or poor cerebral circulation resulting from actual heart disease and failure generally in individuals in whom such mental or nervous trouble is rather easily induced in such cases satisfactory results from cardiac therapy so far as the heart and general circulation are concerned usually improve also the nervous and mental state but may not cure it Mental disorders and nervous instability that are brought to light by heart failure or by cerebral anoxia of other cause such as congenital heart disease with venoarterial shunt are simply latent troubles that tend to recur under other strains than heart failure and often progress to a permanent state of mental or nervous derangement A psychosis resulting from too much digitalis has been reported but not confirmed it is almost certain that such a psychosis is precipitated by faulty circulation rather than by the drug It is true however that sedative hypnotic and narcotic drugs given to cardiac patients may induce acute psychoses as they may in patients with other diseases or indeed in normal persons in such cases paraldehyde (2 to 3 drachms 8 to 12 cc, by mouth by rectum or intramuscularly to be repeated in three or four hours if necessary) is the best hypnotic though not infallible Acute psychoses have been temporarily induced in some patients rapidly dehydrated by vigorous diuresis

Hypochondriasis is a fairly frequent disorder and so far as the heart is concerned may be based on the occurrence or belief of the occurrence of heart disease in other members of the family or in friends with fear of development of similar trouble in the individual himself or on a slight symptom like palpitation from a premature contraction or on mild neurocirculatory asthenia (effort syndrome) or finally on the knowledge of the possession of a systolic murmur which may be wholly unimportant It may be a very distressing condition difficult to treat and requiring the aid of a psychiatrist or on the other hand it may be controlled easily by careful examination and reassurance

Hysteria may assume a cardiac phase without either symptoms or signs of cardiac nature After cardiovascular examination the treatment of the underlying psychiatric disorder should be turned over to expert hands

Schizophrenia (*dementia praecox*) may be associated or aggravated by heart disease as in a patient of my own with congenital patency of the ductus arteriosus of high degree with intense continuous machinery murmur and thrill who constantly reiterated her displeasure at having within her a woman who plotted against her with a roar of machinery Schizophrenia is however infrequently associated with heart disease and the protected life of its victims seems to guard them from early onset of the so-called degenerative types of heart disease Special shock therapy as by the use of Metrazol or electricity for this

or other psychoses rarely if ever hurts the normal heart except for the induction of temporary disturbances of rhythm in some cases slight unimportant changes in the electrocardiogram have also been noted

General paresis, a disease of the central nervous system due to syphilis is frequently complicated by syphilitic aortitis it has been estimated that about 20 per cent of these paretics are so affected

Senile dementia is often attended by coronary heart disease in keeping with the widespread arteriosclerosis that is present but the sheltered invalid existence renders the prognosis better and symptoms fewer than in the average individual with coronary heart disease On the other hand the mental state may render the diagnosis and treatment of angina pectoris myocardial infarction and early stages of congestive heart failure difficult or in some cases impossible as indicated by the significant finding of cardiac rupture in a majority of cases (16 out of 22) of myocardial infarction in the Massachusetts State Psychopathic Hospitals only 2 of the cases had been diagnosed as coronary occlusion during life (Jetter and White, 1944)

## BIBLIOGRAPHY

### NEUROCIRCULATORY ASTHENIA CARDIAC NEUROSIS AND PSYCHOSIS

- Cannon W B "The Mechanism of Emotional Disturbance of Bodily Functions" *New England J Med* 1908 CXCVIII 877
- Craig H R and White P D Etiology and Symptoms of Neurocirculatory Asthenia Analysis of One Hundred Cases with Comments on Prognosis and Treatment" *Arch Int Med* 1914 LIII 633
- DaCosta J M On Irritable Heart A Clinical Study of a Functional Cardiac Disorder and Its Consequences *Am J M Sc* 1871 LXI 17
- Grant, R T "Observations on the After Histories of Men Suffering from the Effort Syndrome" *Heart* 1925 XII 121
- Lewis T *The Soldier's Heart and the Effort Syndrome* Paul B Hoeber Inc New York 1919 2nd ed Shaw and Sons London 1940
- Myers A B E *On the Etiology and Prevalence of Diseases of the Heart Among Soldiers* J Churchill & Sons London 1870 p 22
- Oppenheimer H S Levine S A Morrison R A Rothschild M A St Lawrence W and Wilson F N Illustrative Cases of Neurocirculatory Asthenia" *Mil Surgeon* 1918 XLII 711
- Parkinson J "Effort Syndrome in Soldiers" *Brit M J* 1941 I 545
- Stead E A Jr and Warren J V Clinical Significance of Hyperventilation Role of Hyperventilation in Production Diagnosis and Treatment of Certain Anxiety Symptoms" *Am J M Sc* 1943 CCVI 183
- Viklo L E "Cardiac Neurosis Associated with Rheumatic Valvular Heart Disease" *Am Heart J* 1926 I 539
- White P D The Soldier's Irritable Heart *JAMA* 1942 CXVIII 270
- White P D and Jones T D Heart Disease and Disorders in New England" *Am Heart J* 1928 III 302
- Williams J C *Practical Observations on Nervous and Sympathetic Palpitation of the Heart Particularly as Distinguished from Palpitation the Result of Organic Disease* Longman Rees Orme Browne and Co London 1836
- Practical Remarks on Palpitation and Other Functional Diseases of the Heart* J Churchill London 2nd ed 1852

Wood, P "DaCosta's Syndrome (or Effort Syndrome)" *Brit M J* 1941 I 767 805 845

*Recent References (1944-1950)*

- Carlotti, J Cohen M E and White P D "The Heart Size in Neurocirculatory Asthenia, Effort Syndrome or Anxiety Neurosis" *Am Heart J* 1947 XXXIV 55.
- Chapman W P Cohen M E and Cobb S "Measurements of Levels of Heat Stimulus Perceived as Painful and Producing Wince and Withdrawal Reactions in Patients with Neurocirculatory Asthenia, Anxiety Neurosis or Effort Syndrome and in Control Subjects" *J Clin Investigation* 1946 XXV 890
- Cobb S Cohen M E and Badal D W "Capillaries of Nail Fold in Patients with Neurocirculatory Asthenia (Effort Syndrome Anxiety Neurosis)" *Arch Neurol & Psychiat* 1946 LVI 643
- Cohen M E "Studies of Palmar Hand Sweat in Healthy Subjects and in Patients with Neurocirculatory Asthenia (Anxiety Neurosis Neurasthenia Effort Syndrome) with a Description of a Simple Quantitative Method" *Am J M Sc* 1950 CCXX, 496
- Cohen M E Consolazio F and Johnson R E "Blood Lactate Response During Moderate Exercise in Neurocirculatory Asthenia Anxiety Neurosis or Effort Syndrome" *J Clin Investigation* 1947 XXVI, 339
- Cohen M E Johnson R E Champan W P Badal D W Cobb S and White P D "A Study of Neurocirculatory Asthenia Anxiety Neurosis Effort Syndrome" Final Report to the Committee on Medical Research, Office of Scientific Research and Development, Washington D C 1946
- Cohen M E and White P D "Studies of Breathing Pulmonary Ventilation and Subjective Awareness of Shortness of Breath (Dyspnea) in Neurocirculatory Asthenia" *J Clin Investigation* 1947 XXVI 520
- Cohen M E White P D and Johnson R E "Neurocirculatory Asthenia Anxiety Neurosis or the Effort Syndrome" *Arch Int Med* 1948 LXXXI, 260
- Hauptmann A. and Myerson, A "Studies of Finger Capillaries in Schizophrenia and Manic Depressive Psychoses" *J Nerv & Ment Dis* 1948 CVIII 91
- Jetter W W and White P D "Rupture of the Heart in Patients in Mental Institutions" *Ann Int Med* 1944 XXI 783
- Wheeler E O White P D Reed E and Cohen M E "Familial Incidence of Neurocirculatory Asthenia (Anxiety Neurosis Effort Syndrome)" *J Clin Investigation* 1948 XXVII 562
- "Neurocirculatory Asthenia (Anxiety Neurosis Effort Syndrome Neurasthenia) A Twenty Year Follow up Study of 173 Patients" *JAMA* 1950 CXLII 878
- Wheeler E O Williamson C S and Cohen M E "Observations on the Emotional and Symptomological Effects of Telling Adults That They Might Have Heart Disease" *J Clin Investigation* 1950 XXIX, 852
- White P D Cohen M E and Chapman W P "The Electrocardiogram in Neurocirculatory Asthenia, Anxiety Neurosis or Effort Syndrome" *Am Heart J* 1947 XXXIV 390



## OTHER ETIOLOGIC FACTORS AND RELATIONSHIPS

---

**Neoplasms** Among the rare and relatively unimportant causes of heart disease are cardiovascular neoplasms. It is doubtless because of their rarity and pathologic interest that they have been so often reported in the medical literature. All kinds of tumors, both primary and secondary, including malignant lymphoma (Hodgkin's disease, lymphoblastoma) have been found in the heart and pericardium. Metastases from malignant disease elsewhere are much more numerous than primary malignancy. Mahaim has written in recent years (1945) an authoritative book on the subject of cardiac tumors and polyps.

Primary tumors of the heart have been reported to occur about once in 2,000 cases that come to necropsy (0.05 per cent). 75 per cent of such tumors are benign (Lymburner, 1934). On the other hand, metastatic malignancy of the heart and pericardium has been discovered in 118 out of 11,100 consecutive cases autopsied at the Cleveland City Hospital from 1919 to 1939 (1.1 per cent). These metastatic malignancies involving the heart and pericardium made up 10.9 per cent of the 1,082 cases of malignant disease in the whole series and were especially common with carcinomas of the bronchus and of the breast which were found in 48 per cent of the cardiac and pericardial cases (Scott and Garvin, 1939). In another series, metastatic lesions in the heart were discovered about once in 200 cases of malignant disease elsewhere in the body (0.6 per cent) (Lymburner, 1934). Of primary tumors, there have been reported in the order named: most commonly myxoma, sarcoma, and rhabdomyoma; less often carcinoma, fibroma, lipoma, angioma, cystoma, papilloma, teratoma, and epicardial epithelioma. In 1922, a review of the literature revealed the record of 150 cases of primary tumor of the heart, 40 of which were sarcomas. A new case of primary sarcoma was reported then (Goldstein). During the next 25 years, over 50 more cases of primary cardiac tumor were reported, including myxoma, carcinoma, sarcoma, and xanthoma. The new case of primary sarcoma of the heart reported by Wier and Jones in 1941 raised to 76 the total number of such tumors then on record. More cases

were added in 1948 (Shelburne Halhuber and Kapferer) and a primary sarcoma of the abdominal aorta has also been reported (Nencki 1946) In a reported series of 3 000 consecutive autopsies there were no primary heart tumors but there were 6 cases of secondary cardiac neoplasm originating twice in the uterus and once each in rectum kidney gallbladder and lung (Thorel 1903 1907) this illustrates not only the preponderance of secondary cardiac



FIG 117 Metastatic melanotic sarcoma showing many lesions throughout the myocardium of both ventricles and septum of the heart (Kindness of Dr Pedro Castillo Havana Cuba )

tumors but also the multiplicity of the original tumor sites Among cardiac metastases malignant melanoma (Figure 117) has held a prominent place 4 cases having been added in 1939 (Moragues) to the 23 on record and at least 5 more have been reported since (Raven 1948 Lefkowitz 1948 Ritz 1949) A recent report of 30 cases of metastatic cardiac tumors has been published by Piotti (1949) consisting of 23 carcinomas and 7 sarcomas in 17 men and 13 women the diagnosis was correctly made ante mortem in 20 of the cases Eight of the primary tumors were bronchial (6) or pulmonary (2) Tachycardia was the most common sign

Primary sarcoma of the pericardium has been reported in 11 cases 10 collected in 1931 (Yater) and one added later (Steuer and Higley 1935) Metastatic pericardial malignancy secondary to a lung tumor may be very,

extensive (Figure 118) Bloody pericardial fluid is commonly found in malignant disease of the pericardium

Any heart chamber may be the site of neoplasm whether primary or secondary but the right chambers are more often involved than the left doubtless because the tumor is so often spread by the blood stream (Lymburner 1934) even the node of Tawara can develop its neoplasm (Mahaim 1942)

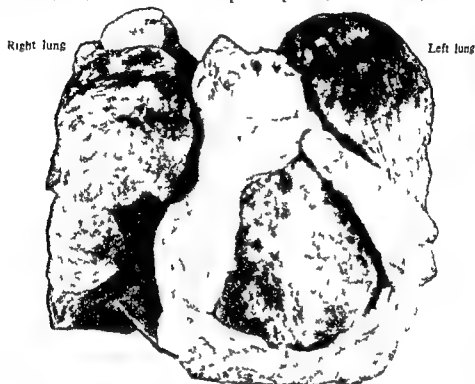


FIG 118 : Photograph showing extensive malignancy (carcinoma) of the pericardium secondary to a tumor which is visible at the apex of the right lung The heart is somewhat compressed by the massive cancer surrounding it (Kindness of Drs Tracy Mallory and Benjamin Castleman Massachusetts General Hospital Boston )

Only rarely has it been possible to diagnose neoplasms in the heart before death in the past but that is changing now as noted in Piotti's report above As a rule they are relatively unimportant metastases or primary growths discovered incidentally at postmortem examination in persons dying of malignant or other disease elsewhere than in the heart In rare cases they may weaken the heart wall or produce heart block (atrioventricular or intraventricular) or other arrhythmias or embarrass the circulation otherwise by their size causing cyanosis and even simulating valvular disease by obstructing the valve ostia hence in heart trouble of unknown cause they should be thought of and looked for clinically Roentgen ray examination (showing unexpected heart size and shape) the discovery by electrocardiogram of atrioventricular or bundle branch block or T wave changes not otherwise explained the find

ing of a pericardial friction rub or effusion apparently not the result of infection and the presence of neoplasms elsewhere afford the most suggestive evidence. The prognosis is serious except in the case of a few benign tumors and yet as a rule the individuals affected die of other than the cardiac involvement. There is at present no adequate treatment for cardiac neoplasms; surgery, radiotherapy, and chemotherapy of the tumor cells have not yet been sufficiently developed, although life may be somewhat prolonged by radiotherapy in certain cases, especially in those of malignant lymphoma.

**Poisoning other than by infections.** The effect of infectious toxins on the heart has already been discussed; there remains the consideration of the effect of other poisons or possible poisons. Fortunately, any destructive myocardial effect of *heavy metals* as in arsenic, bismuth, and mercury poisoning is very rare and fatal results come as a rule not from the cardiac involvement but chiefly from the damage to other organs, in particular to liver and kidneys. Mercury, now in very common use as a diuretic, has been surprisingly well tolerated, but in rare instances it has caused renal damage and, in nearly unique cases, collapse or sudden death of uncertain (perhaps cardiac) nature. Phosphorus poisoning may depress the *T* waves and the *ST* segments (Dathé and Nathan 1946). There has been no observation of direct injury to the heart in lead poisoning. *Illuminating gas* (carbon monoxide) has been reported to have caused necrosis in the myocardium and in the media of cerebral arteries of persons dying of its effect (Grunewald 1926) and electrocardiographic abnormalities such as a *v* block (Almgren 1946, Casolo 1947). Certain other poisons taken as food have been found to influence the heart; for example, the mushroom *Amanita phalloides* has been reported to have been the probable cause of temporary right bundle branch block (Hyman 1928). Central American snake venom has been noted to depress the *T* waves and *ST* segments and to prolong the *QT* interval (García Carrillo 1947) and the scorpion's bite can cause tachycardia and arrhythmias (Celoria and Sloer 1948).

**Drug poisoning.** The drug most likely to poison the heart is *digitalis* itself, which is used so often to control heart failure. If given in excessive dosage, digitalis may easily irritate the heart, producing premature beats (extra systoles), atrioventricular block, sinoatrial block, or even atrial standstill, atrial paroxysmal tachycardia, atrial fibrillation, ventricular paroxysmal tachycardia, with or without alternation in direction of the ventricular complexes in the electrocardiogram, and in rare instances ventricular fibrillation and death. La Due (1942) has produced myocardial necrosis, fibrosis, and atrophy in 44 per cent of dogs which he subjected to daily intravenous doses of large amounts of digitalis. It is very helpful to follow electrocardiographically the administration of saturating dosage of digitalis, thus watching for some of the signs of poisoning, as indicated by excessive inversion of the *T* waves and especially of the *ST* segments, by prolongation of the *PR* interval (atrioventricular block), by the appearance of ventricular premature beats occurring bigeminally, and if the poisoning is of dangerous degree by the onset of ven-

tricular paroxysmal tachycardia. Such electrocardiographic signs indicate that a considerable percentage of the lethal dose of the drug has already been administered. Other indications of digitalis poisoning should also be looked for, namely anorexia, nausea, vomiting and visual disturbances (cloudy or colored vision). Diarrhea is a less common toxic effect of the drug. The possibility of a deleterious toxic influence of digitalis on the heart is an important reason for not administering the drug carelessly. Digitalis poisoning became more common in this country for a while on two occasions in recent years: first after the strength of American preparations was raised some 30 to 50 per cent during the period of the eleventh edition of the *U S Pharmacopeia* 1936 to 1942 (Bland and White 1941) dropping since the publication of the twelfth edition in 1942 to a 16 to 30 per cent increase over the strength of the standard unit prior to 1937 and second when digitoxin began to be used more freely with large daily rations of 0.2 mg or more (see Chapter 30). Fortunately serious poisoning of the heart by digitalis given by mouth is unlikely to happen because of the emetic effect of large doses.

*Quinidine sulphate* another very helpful drug that may poison the heart, has been used considerably in recent years in the treatment of cardiac arrhythmia, particularly atrial fibrillation. This medicine may have a harmful effect on the heart as well as the beneficial effect of abolishing atrial flutter and atrial fibrillation. Such harmful effect is shown by the presence of sinoatrial depression, intra atrial block and intraventricular block and rarely premature contractions, paroxysmal tachycardia (atrial or ventricular) and even ventricular fibrillation or standstill. It is probable that the rare cases dying suddenly during quinidine therapy have for the most part suffered direct fatal quinidine effects on the heart, in particular total standstill due to paralysis of both sinoatrial and atrioventricular nodes. The drug should be employed only with great care if large doses are administered and then only under close observation with electrocardiographic control. Quinidine therapy will be discussed further in Chapter 33.

Other drugs are less frequently the cause of heart trouble although occasionally when one of them is given too vigorously such as *arsenic* in large dosage in the treatment of syphilis, heart failure may be precipitated. The *salicylates* including aspirin may cause serious poisoning and even death in rare cases which show postmortem petechial and larger hemorrhages scattered throughout the body and focal necroses (Krasnoff and Bernstein 1947).

The intravenous therapeutic use of *calcium* in high concentration can prolong systole, depress the cardiac pacemakers and conduction tissue (to cause bradycardia and heart block), and increase the excitability of the ventricular muscle (to produce ectopic beats) (Clark 1941). *Potassium* in large dosage elevates the *T* waves of the electrocardiogram and widens the *QRS* waves while tending to produce abnormal peripheral sensory reactions (paresthesia). It should be employed cautiously in renal disease since the poisonous concentration of potassium in the blood is a common occurrence in renal insufficiency (Thomson 1939 Keith et al 1942).

Tarail (1948) noted that electrocardiographic changes begin to appear when the concentration of serum potassium lies between 6.8 and 7.6 milliequivalents per liter and are consistently found at amounts greater than 7.8 mEq/L. A fatal concentration in man is over 10.0 mEq/L when diastolic standstill occurs with generalized flaccid paralysis (Finch et al. 1946). Sodium and calcium salts, blood and glucose may correct the effects when not extreme. Low potassium blood levels can also affect the electrocardiogram flattening the T waves and prolonging systole.

*Metrazol* used to cause convulsions in psychopathic states may induce extrasystoles of little import. *Ergotamine* raises and *adrenaline* lowers the T waves through their vagal and sympathetic effects respectively (Hartwell et al. 1942) and *morphine* has long been known to produce vagal effects on the heart with slowing of the rate, delay in conduction, lowering of the R waves and raising of the T waves (Einthoven and Wieringa 1912). *atropine* neutralizes this effect and when given alone lowers the T waves (Hartwell et al. 1942). Various other drugs may produce electrocardiographic changes for example *emetine* (for amebiasis) which lowers the T waves and delays conduction and *antimony* (Fusidin and tartar emetic for schistosomiasis) which lowers the T waves and prolongs systole. The *sulfonamides* may cause myocardial necrosis in rare cases but penicillin does not do so.

Finally *chloroform* as an anesthetic has long been known to have a poisonous effect on the heart causing extrasystoles and even ventricular fibrillation in animals and probably by this same mechanism causing sudden death in rare instances in man. *chloroform* and the newer related anesthetic *cyclopropane* are therefore far more dangerous anesthetics than ether and most other preparations especially if the heart is already diseased and irritable.

There are a few substances used widely by mankind for pleasure or stimulation or because of habit that have as a rule but little deleterious effect on the heart. The literature is full of conflicting statements about their harmless or pernicious influence. Such substances are alcohol, tobacco, tea and coffee.

*Alcohol* in strong concentration and large amounts can perhaps injure the myocardium but certainly to a far less extent than more sensitive organs like the liver and brain. In small or moderate amounts it has no harmful effect at all but rather a vasodilating action which relieves or prevents angina pectoris. Small quantities of alcoholic beverages through their relaxing effect may benefit individuals who are depressed or under nervous tension and it is even possible that regular daily use of light wine or beer in moderation may favor the maintenance of good health. In fact it has been noted by several observers (Cabot 1904, Leary 1931) that arteriosclerosis is rare in cases of excessive alcoholism suggesting a protective influence in that respect though less than nothing is gained if liver, brain and morale are seriously damaged in the process. The cardiovascular reaction following acute alcoholism is moreover often unfavorable producing neurocirculatory asthenia, paroxysmal arrhythmias, increase in angina pectoris or precipitation of congestive failure in

cardiac patients Finally a considerable use of alcoholic beverages does not protect a person from serious coronary heart disease even in the forties as I have found in the case of several patients

*Tobacco* varies greatly in its effect according to the individual and also according to the tolerance produced by habit It causes no actual heart disease but it may in large amounts or in susceptible persons excite sinoatrial tachycardia premature contractions or paroxysmal tachycardia, and in extreme cases paroxysmal atrial fibrillation Palpitation may be caused by these arrhythmias In the majority of individuals particularly hypertensive patients the blood pressure (both systolic and diastolic) is raised appreciably and even the metabolic rate In a few individuals with coronary heart disease the use of tobacco has been known to precipitate or to aggravate angina pectoris and to cause tachycardia temporary changes in the *T* waves of the electrocardiogram, and a harmful effect on the coronary circulation In fact in one healthy young man the inhalation of tobacco smoke has been observed temporarily to cause dizziness and inversion of the *T* waves in Leads 1 and 2 of the electrocardiogram so that they resembled for a few beats the *T* waves of coronary heart disease (Graybiel Starr and White 1938), whether this change is to be attributed to excessive sympathetic nerve stimulation to coronary arterial constriction or to a direct toxic myocardial effect we do not know but we are inclined to accept the first of these explanations Various recent investigations (Roth et al 1944, Boyle et al 1947 Levy et al, 1948 Mathers et al 1949) have compared the effects of inhaling tobacco smoke with the injection of nicotine and have found them to be similar with increase of heart rate and blood pressure and lowering of the *T* waves of the electrocardiogram tachycardia is the simplest gauge of hypersensitiveness to tobacco (nicotine) Thus there is after all such a condition as a tobacco heart but it is a state of functional derangement of the heart and circulation and not organic heart disease When the so called denicotinized tobacco which contains only  $\frac{1}{3}$  to  $\frac{1}{4}$  or less of the amount of nicotine found in ordinary tobacco is used the heart is much less likely to be disturbed in individuals who are sensitive to the plant Tobacco also causes a peripheral vasoconstriction with lowering of the skin temperature (Weatherby 1942) and has been suggested as a factor in causing thromboangitis obliterans a disease of youth and middle age of unknown etiology to be discussed in Chapter 28 The chief disadvantage of tobacco in my experience has been the induction of cardiospasm and even gastritis as disagreeable complications in my cardiac patients or as trouble simulating the angina pectoris of coronary heart disease Because of the fact that tobacco (nicotine) is, in most persons a pressor agent it is wise to avoid its use in the presence of hypertension Incidentally it is of interest that alcoholic beverages do not neutralize the vasoconstricting effect of tobacco (Roth and Sheard 1947)

*Tea and coffee* do not cause heart disease but by nervous stimulation they are frequently the cause of increased heart rate and palpitation and in some

susceptible individuals of premature beats or paroxysmal tachycardia on the other hand they may be helpful in cases of mild Cheyne Stokes respiration

A few years ago much excitement was engendered by the discovery of some lithium poisoning secondary to too liberal use of lithium chloride as a substitute for sodium chloride in low sodium diets for congestive heart failure in particular. Few serious cases were found among many thousands but unfortunately this excellent taste substitute was largely abandoned whereas under proper control and in small dosage (e.g. a few drops of a 25 per cent watery solution amounting to not more than 0.05 gm a day) it is quite harmless and helpful. The symptoms of lithium poisoning are not cardiac but include in particular weakness of muscles and mental confusion.

Finally poisons may be generated in the body itself to irritate or damage the heart. The most frequent well marked example of this is in the case of uremia where abnormal heart action and distorted electrocardiograms have sometimes been found doubtless the result of the toxic effect of the high content of potassium in the blood. Irritation of the heart as shown by the appearance of premature beats may sometimes be only a reflex nervous manifestation which doubtless explains in large part the relationship of such conditions as indigestion as well as of most focal infections to cardiovascular symptoms. A slow pulse due to sinoatrial bradycardia apparently a vagal effect is occasionally prominent in cases of catarrhal jaundice the toxic effect of severe hepatic insufficiency is manifested especially by stupor and depressed respiration.

**Disorders of nutrition** **Avitaminosis** **Obesity** **Fatty infiltration and fatty degeneration** **Gout** Much has been said about malnutrition and the harmful effects of avitaminoses and much of it is true but overemphasis on these conditions has had two harmful results (1) the excessive use of all kinds of expensive vitamin preparations and (2) the relative neglect of overnutrition which with or without obesity is doubtless more injurious to more persons than is undernutrition. It may well be that especially in the U.S.A. today overnutrition with its common companions diabetes coronary atherosclerosis and hypertension is on the way to becoming a major threat to the health of the people. An important consideration about malnutrition especially the avitaminoses is that the deficiency is only rare in one food element whether protein vitamin B<sub>1</sub> vitamin C or vitamin D or other factor the deficiency is almost invariably multiple.

**Beriberi** a disease which is primarily the consequence of vitamin B<sub>1</sub> deficiency (tropical avitaminosis) has been shown to cause hydropic degeneration (intracellular edema) of the myocardium particularly of the right ventricle with cardiac dilatation and failure in rare cases. Electrocardiograms have shown in such cases small complexes negative T waves in Lead I and slight aberration of the ventricular complexes. Beriberi was once a common disease in the Orient but it has been much reduced in the last generation by



change of diet from that of polished rice low in the essential vitamins in the Occident beriberi has never been common but it is occasionally seen in severe alcoholism in markedly restricted intake of food as in Negro infants and young children reported by Waring (1929-1938), and in a few individuals with severe gastrointestinal disorders or psychiatric conditions resulting in semistarvation with avitaminosis. Heart disease with enlargement and peripheral vasodilatation with rapid blood flow are found complicating only the more severe cases of beriberi often attended by a polyneuritis. Beriberi is one of the few conditions (another is arteriovenous fistula) which may result in congestive heart failure even though there continues to be an increased cardiac output (Weiss and Wilkins 1937, Burwell and Dexter, 1947). As a complicating factor in other conditions especially in heart failure itself with poor appetite and malnutrition avitaminosis of mild to moderate degree may cause additional trouble and require specific therapy. The edema of wet beriberi is largely the result of congestive heart failure but may also be favored by malnutrition with low serum protein. Relief is obtained primarily neither by digitalis nor by diuretics but by the administration of antineuritic vitamin B<sub>1</sub> intravenously in severe cases but by mouth with success in most patients.

*Scurbutus* (scurvy), due to lack of vitamin C carries with it a tendency to hemorrhage which may involve the heart and pericardium as well as other parts of the body the heart muscle is said to show degeneration in scurvy.

*Rachitis* (rickets) due to lack of vitamin D when very severe is also associated with abnormality of the heart consisting chiefly of dilatation and failure in a series of eleven children dying suddenly with rachitis each child showed at postmortem examination left ventricular dilatation (Meixner 1928).

*Pellagra* although an important and common deficiency disease has not been found to be associated with any specific cardiac pathologic abnormalities except for changes in the T waves of the electrocardiogram (Rachmilewitz and Braun 1944). Circulatory troubles found in such cases are to be ascribed for the most part to lack of vitamin B<sub>1</sub> or to the hypoproteinemia of starvation or to a coincident heart disease. Nicotinic acid is the specific treatment for pellagra but all of the vitamin B group should also be given to cover the combined deficiencies present.

*Starvation* may cause generalized edema in victims of famine such edema may be the result of depression of renal excretion of sodium (Berkman 1950) or caused by disturbed osmotic pressure due to low blood protein (albumin) as in cases of 'nephrosis' and is not a manifestation of cardiac failure. The critical level of protein in the blood serum below which nutritional edema appears is about 5 gm per 100 cc the albumin globulin ratio is often reversed. Adequate diet especially rich in protein and vitamin B<sub>1</sub> because of a frequently associated avitaminosis quickly clears up this edema. Starvation decreases the heart size cardiac rate and output blood pressure and electrocardiographic voltage while increasing the duration of systole (Ellis 1946 Simonson et al 1948), it has been estimated that for a loss of 30 per cent in body weight there is a loss of 20 per cent in the heart weight (Keys 1948).

*Obesity* may or may not be attended by heart disease. It is common for obese individuals because of lack of physical training and fitness and because of their excessive weight to develop the effort syndrome easily but this does not signify heart disease. It is however now well known that obese persons have more hypertension and atherosclerosis and live shorter lives than do persons who are lean or of average weight and yet overnutrition continues to be the rule in this country. Most persons add 20 pounds or more of weight after the age of 25 years and such increased weight is due to the deposition of fat not just under the skin but in the liver as well and in the coronary artery walls. It would seem to be common sense to avoid adding fat when there is already good nutrition.

There is a greater tendency also for obese individuals than for thin persons to store fat in and about the heart especially in the interventricular and atrio-ventricular grooves and over the surface of the right ventricle into the musculature of which it may actually slowly penetrate splitting the wall and favoring atrophy of the myocardium and even rupture or failure of the right ventricle. Fat may be deposited subendocardially especially in the course of the atrio-ventricular conduction system in an amount said to be sufficient to cause pressure and atrophy and under special strain even sudden death. Of these last mentioned effects of fat in and on the heart we have however no proof.

Two common important sources of error in the estimation of heart size by roentgen ray arise as the result of obesity and fat deposits. In a stout person especially when there is much abdominal fat the diaphragm tends to be high in position and the heart placed horizontally. Such a horizontal heart shadow shows an increase above the average normal both in transverse diameter and in area (see Chapter 7). Hence a correction must be made in such cases in the estimation of heart size. When because of the horizontal heart position the transverse diameter approaches the long diameter in measurement (usually it averages 1.5 cm less) 1 to 2 cm may be subtracted from the transverse diameter and about 25 sq cm from the area in calculating the heart size. Also in such cases the aorta tends to be kinked by the upward pressure and looks much wider in the anteroposterior view than it actually is sometimes resulting in an erroneous diagnosis of aortic dilatation. Views during deep inspiration and also with the subject in the oblique positions help to prevent errors of roentgen ray interpretation in obese individuals.

The other source of error in roentgen ray interpretation arises from the presence of a triangle of fat usually some 2 to 3 cm wide at the pericardial diaphragmatic angle on the left just beyond the cardiac apex (Figure 7 shown on page 39) this is more common in but not limited to obese persons. An extrapericardial layer of fat at the right heart border may also cast an appreciable and sometimes confusing shadow. Unless care is taken the transverse heart diameter and the area may be erroneously measured and misinterpreted (McGinn and White 1936).

That there is an actual *fatty heart* (*cor adiposum*) consisting of fatty infiltration as described above has been proved by pathologic studies but the

clinical significance of the condition is not clear, the truth probably rests between the two extreme views that the fatty heart is a common and dangerous condition and that it does not exist at all. Still more doubtful is the association of the cor adiposum with general obesity, they often are associated but there are also frequent exceptions the fatty heart being found in the absence of obesity and obesity being found without the fatty heart. More study is needed to solve this problem.

*Fatty degeneration of the heart* may ensue in cases of marked fatty infiltration but it is strictly a different condition and results as a rule more or less acutely from the toxic influence of infectious or noninfectious poisons and from the cutting off of the blood supply to the myocardium by severe anemia (see below) or by the narrowing or occlusion of the coronary arteries. It is therefore not primarily related to obesity.

*Gout* is often associated with excessive atherosclerosis and coronary heart disease which in the younger age group is frequently attended by an abnormally high content of uric acid in the blood but there strictly is no such entity as a gouty heart.

**Blood diseases.** Serious cardiac dilatation may occur with high grade anemia and may cause functional insufficiency of the mitral and of the tricuspid valves and in rare cases also of the aortic valve. In severe anemia of any type the circulatory rate is increased with elevation of pulse pressure, stroke volume, minute volume, cardiac rate and output and oxygen consumption and with decrease in the arm to tongue circulation time. When the hemoglobin content drops below 25 per cent (3.5 gm) the cardiac dilatation may become extreme and congestive heart failure may appear without pre-existing heart disease. In one series of 10 patients with very severe anemia (Tung et al. 1937) 6 showed marked congestive failure with no other discoverable cause than the anemia. Treatment for and recovery from the anemia usually results in a disappearance of the congestive failure and a return of the heart size toward or to normal. Anemia is one of the four important clinical conditions in which congestive heart failure is attended by an increased cardiac output, the other three being beriberi, thyrotoxicosis and an arteriovenous fistula.

Electrocardiographic abnormalities are also common in severe anemia. In one group of 76 anemic patients 23 showed abnormal records (Szekely, 1940) and in another of 45 cases 10 had such electrocardiograms (Ellis and Faulkner, 1939). The abnormalities consist of flattening or inversion of the T waves, depression of the ST segments and a tendency to low voltage of the QRS waves. With correction of the anemia the electrocardiogram usually returns to normal.

It may be concluded that the heart trouble in anemia is due to the combination of the myocardial anoxia and the increased work of the heart.

In *hyperchromic* commonly *pernicious anemia* years ago before the institution of specific liver therapy the heart was commonly found at postmortem examination hypertrophied and dilated with fatty degeneration of the myocardium in streaks farthest from the fresh blood supply that is at the venous

ends of the capillaries giving rise to a curious gross appearance which was called the tiger or 'tiger lily heart'. Although it was the anemia and not the heart trouble that was usually responsible for death, congestive failure and angina pectoris were seen in rare cases. Now that specific remedies have been introduced for pernicious anemia, protection of the heart has been possible against the changes noted above. In rare cases, however, angina pectoris has apparently been precipitated during specific treatment of pernicious anemia, probably through the accompanying increase in blood volume.

*Hypochromic (secondary) anemia* if slight has no deleterious effect on the heart, but if it is severe there may result the same fatty changes, dilatation and hypertrophy that were at one time common in primary pernicious anemia. Also angina pectoris may occur in rare cases even in the absence of coronary disease (Elliot 1934). Systolic murmurs at apex and base are common in severe anemia of any type due to left ventricular dilatation with mitral regurgitation and to dilatation of the aorta and pulmonary artery. Even diastolic murmurs, mitral and aortic and possibly even pulmonary are not rare in severe cases; the pathogenesis of such murmurs is undoubtedly concerned with the dilatation of the heart. With a much dilated left ventricular cavity and a rapid blood flow such as is usually found in marked anemia, a mitral diastolic murmur is produced by a relative mitral stenosis though the mitral valve itself is normal or even slightly dilated, while weakness of the aortic and pulmonary valve rings may result in their stretching with resulting regurgitation. Such murmurs tend to come and go according to the functional state of the heart. Gunewardene (1935) has called attention to the frequent wrong interpretation, labeled mitral stenosis, of cardiac dilatation in severe anemia in India.

In *sickle cell anemia* not only may the heart resemble the rheumatic heart with its enlargement and various murmurs but the course of the exacerbations of the disease over a period of years may resemble rheumatic fever; the pains, however, involve the long bones rather than the joints and are not relieved by salicylates (Klinefelter 1942).

With the reverse condition *polycythemia* (or erythremia) the increased bulk of blood is an added burden for the circulation but strain on the heart is largely prevented by peripheral vasodilatation. The capillaries are uniformly found dilated in cases of polycythemia, whether primary (Vaquez-Osler disease) or secondary to congenital heart disease or chronic pulmonary disease. Vascular lesions, thromboses especially, are occasional accompaniments of polycythemia. A study of 98 cases of polycythemia vera and of 35 cases of relative polycythemia by Norman and Allen (1937) revealed in about a third of the cases a variety of vascular complications—erythromelalgia, coronary thrombosis with myocardial infarction, angina pectoris, occlusive disease of the peripheral arteries, cerebral hemorrhage or thrombosis, intra-abdominal vascular thrombosis, phlebitis and vasomotor neuroses.

Oxyhemoglobin may be limited in the blood by the existence of methemoglobinemia acquired as in the case of carbon monoxide or acetanilid poison.

ing or congenital as in the case of 5 members of one family reported by Gibson and Harrison (1947) it is important to distinguish the cyanosis in such cases from that of cardiac or pulmonary disease and from the reduced silver in the skin in argyria

In *lymphatic leukemia* and less often in *myelogenous leukemia* the myocardium as well as many other organs and tissues of the body may be found infiltrated with the abnormal leukocytes but this finding is merely a minor part of these fatal diseases. Hodgkin's disease (malignant lymphoma or splenic anemia) is discussed earlier in this chapter under the heading Neoplasms it may be attended by severe anemia

**Trauma** Injuries of all varieties may involve the cardiovascular apparatus in any part—heart pericardium great vessels arteries or veins. Injuries of blood vessels are very frequent and even trauma of the heart itself is not at all rare. There may be penetrating wounds of the heart by gunshot bomb or shell fragments, knife dagger sword bayonet or other instrument such as were seen by the thousands during both World Wars. Injury may come in directly by contusion from blows or falls by crushing or by intense jarring. Finally there may be spontaneous rupture of valve cusp chordae tendineae papillary muscle atrial or ventricular wall or aorta. When rupture of any sort comes by indirect violence or spontaneously heart disease is usually found to underlie the injury—for example bacterial endocarditis in the case of rupture of valve cusp or chordae tendineae cardiac infarct in the case of rupture of heart wall septum or papillary muscle (see Chapters 21 and 25) and aneurysm or medial necrosis in the case of ruptured aorta (see Chapter 28). Sometimes however even when the trauma does not seem great clean cut rupture (usually linear tears) of heart wall or aorta may occur without any evidence of local disease at postmortem examination such cases are to be explained by an unusual amount of strain exerted at the moment of full distention of heart chamber aorta or valve cusp the tissue in question being perhaps congenitally weak. A defect in the media of unexplained etiology (Erdheim 1929—see Chapter 28) no doubt accounts for some aortic ruptures. The reports of proven cases show that serious or fatal injury can come even to a normal heart or aorta from indirect or direct trauma as in striking the surface of the water in diving without any penetrating wound. The greater the injury the more likely of course is heart damage. See Figure 119 for rupture of papillary muscle.

Contusion or even partial rupture of the heart wall may also occur and because of the usual recovery of such cases may pass notice (Schlomka and Schmitz 1932 Bright and Beck 1935). A steering wheel injury produced by sudden compression of the anterior chest wall of the operator of a motor car by his steering wheel at the time of an accident is doubtless a cause of contusion of the heart (Bright and Beck 1935) but just how common it is we do not know there is considerable danger now of its exaggeration. In these days of claims for compensation for injuries by everything under the sun the steering wheel cardiac contusion is having its share of publicity and has

already become the cause of at least some cardiac or traumatic neuroses. As a matter of fact the heart is a very mobile organ in the chest and is likely to escape injury whether the trauma is penetrating or not, in reviewing cases of wounds of the heart Elkin (1938) noted that in his experience only 2 per cent of penetrating wounds of the chest injured the heart. Contusion or even rupture of the heart has been recognized as an occasional result of blast injuries resulting from bomb explosions in World War II or even as an industrial



FIG. 119 Photograph of traumatic injury to the heart. Anterior papillary muscle of the left ventricle torn from its base (as shown by the arrow) in case of a young man run over by a truck.

hazard (Miller 1947). The only clue to heart muscle contusion in some cases is electrocardiographic evidence of fresh myocardial damage. An electrocardiogram should be obtained whenever possible shortly after any severe thoracic injury. Temporary changes, especially in the T waves, may follow a penetrating or contused lesion of the heart muscle and like the electrocardiogram in acute myocardial infarction aid in the localization of the damaged area.

In the last edition of this book (1944) I wrote that coronary thrombosis with myocardial infarction is not the result of trauma so far as we know at present from the experience of many observers of many hundreds of cases except in a few instances of advanced coronary atherosclerosis and narrowing to start with and in others where because of an incised wound of the heart wall it has been necessary to ligate a major coronary artery in the course of

surgical repair. Since then however a case has been reported of a boy of ten years who succumbed to acute coronary thrombosis involving the left descending artery a few minutes after three rounds of a boxing match. necropsy showed only slight atheromatous changes in the intima (Jokl and Greenstein 1944).

In rare cases recovery may take place after rupture or penetrating wound of the heart especially in the case of the latter injury, if operative relief can be quickly afforded. Many cases of successful healing of sutured wounds of the heart have been reported. There may be no sequelae after such wounds and the heart, years afterward may be found to be carrying on its function in a normal manner. on the other hand serious after-effects may appear. A striking case in a youth has been reported of perforation of the anterior mitral valve cusp (gunshot wound) producing pure mitral regurgitation and followed by enormous enlargement of the heart with hypertrophy and dilatation of all four chambers and death after several years from congestive failure (Adam 1927). In this last mentioned case there was also an adherent pericardium following the hemopericardium produced by the injury but this had little or nothing to do with the cardiac enlargement and failure. Such a coincidental pericardial lesion may complicate any case of cardiac trauma. Another interesting instance is also on record of death from heart failure in the case of a young man 14 months after rupture, by a crushing injury of the cusps of his normal aortic valve (Kissane et al 1936). Heart block has been noted after cardiac trauma (Coffen et al 1941).

Successful suture of wounds of the aorta also has been proved possible as in a case reported by Blalock (1934) and of vena cava too (Barnes 1938).

One of the chief hazards of penetrating wounds of the heart is that of *cardiac tamponade from hemopericardium*. This may come quickly in the course of a few minutes or an hour or so and to the inexperienced eye may simulate shock. The pulse becomes small and rapid with very low pulse pressure and paradoxical character the neck veins become engorged (unless there is a coincident vascular collapse) because of their inability to empty into the acutely constricted or compressed heart and death may ensue shortly unless surgical relief is afforded. The heart wall must of course be sutured to prevent further bleeding, but the emergency measure is paracentesis (or better incision) of the distended pericardium as in a case reported by Rajasingham (1939).

Furthermore *foreign bodies* may enter the heart wall or chambers and remain there for years perhaps with little or no harmful effect. Extraordinary instances have been reported of projectiles migrating to the heart by way of the great veins from distant wounds in thigh abdomen or neck and in two cases (Boeckel 1917 and LaRoque 1926) of projectiles migrating from left ventricle and aorta respectively as emboli to block the femoral artery with resulting gangrene of the leg in Boeckel's case. Another very interesting case has recently been reported by Shapiro (1941) of migration of a hollow needle used for intravenous injection from arm vein into the heart and through the

heart wall to lie eventually in the prepericardial fat between heart and diaphragm

Trauma to the myocardium may result from excessive exposure to the roentgen ray. This has been shown in experimental animals and found at autopsy in a few patients treated by radiotherapy for intrathoracic tumors. Clinical evidence of such injury has not yet, however, been demonstrated convincingly.

Arrhythmias are sometimes induced by trauma but as a rule they are unimportant, temporary, and either subside spontaneously in the course of a few days or weeks or are easily controlled by treatment (see Chapters 32 and 33). This is true even of absolute arrhythmia (atrial fibrillation) which is likely to occasion unnecessary alarm except in rare persons in whom congestive heart failure may be induced by the extra strain of the atrial fibrillation when there is already present chronic heart disease with limited reserve.

*Electric shock*: whether accidental (Koeppen 1940) or induced in the therapy of psychoses (Streit 1941; Hejtmancik, Bankhead, and Hermann 1949) can produce all kinds of disorders of the heart rhythm, but especially extrasystoles. Changes in the *ST* segments and *T* waves have been reported, lowering of the former and at first elevation and later depression of the latter. Electrocuting results in death from (or with) ventricular fibrillation (following quickly after the appearance of extrasystoles and bundle branch block) (Kountz, personal communication 1943).

Finally, the question of the relationship of *occupational hazards* to cardiac trauma is important and often very difficult. Occasionally injuries received during work may traumatize seriously a perfectly normal heart, but as a rule heart symptoms or signs that follow industrial strain or accidents are either merely those of neurocirculatory asthenia or neurosis in sensitive individuals or are due to the precipitation or aggravation of trouble in a heart already damaged or diseased. The decision as to the relative responsibilities of accident or strain and of previous heart disease in the production of symptoms and signs is often a great problem, sufficient to tax the wisdom of the most experienced physician or judge. A most interesting problem of sudden cardiac death on Monday mornings of employees of powder plants when hurrying back to work after being out of the nitrite atmosphere for some 60 hours during the weekend was a case in point (Drinker, personal communication 1935). This hazard was eliminated when the plants were adequately ventilated. Even after an adequate appraisal of the relative responsibilities of trauma or other strain and of pre-existing heart disease in the production of cardiovascular symptoms or signs of disability, it is not always possible to adjust accident or industrial insurance compensation in accord because of faulty local laws or regulations that in some places the decision must be all or nothing instead of a proper percentage of the total. This faulty situation demands correction. Of the greatest importance in this connection is the value of careful routine (annual) cardiovascular examination of all industrial employees.



**Thoracic and spinal deformities** An appreciable and sometimes serious handicap to the action of the heart and circulation may be occasioned by deformities of the thorax or spine particularly marked *kyphoscoliosis*. The strain, however, may be more pulmonary than cardiac with much diminished vital capacity of the lungs but almost always both systems respiratory and circulatory, are involved with resultant pulmonocardiac failure (Chapman Dill and Graybiel, 1939). The heart may be displaced (to the left with right scoliosis and to the right with left scoliosis) and deformed and the great vessels compressed so that left ventricle or right ventricle or both may have increased work to do with resulting hypertrophy and dilatation. Or the restriction of thoracic movement in respiration may result in special strain on the right ventricle such as occurs in the case of the *cor pulmonale*. In badly deformed individuals survival to old age is frequently prevented by the cardiovascular strain as well as by pulmonary complications.

**Marked depression of the sternum** (producing funnel chest or *pectus excavatum*) may in rare cases seriously embarrass the heart by flattening it anteroposteriorly and compressing the right atrium and right ventricle during expiration or by torsion of the great vessels usually however the heart is simply displaced to the left without any particular handicap unless the deformity is extreme with little mediastinal space between sternum and spine. Operative relief is difficult but may be successfully carried out as in the series of cases operated upon by Sauerbruch (Sauerbruch 1931 O'Shaughnessy 1940) and as has been done since 1943 by Sweet at the Massachusetts General Hospital.

The presence of *cervical ribs* may occasion not only trophic disorders and disturbances of the peripheral circulation in the hands somewhat resembling Raynaud's disease and in some cases thrombotic and embolic obliteration of arteries of the arms and hands (Telford and Stopford 1931, Eden 1939) and even subclavian arterial thrombosis and hemiplegia due to cerebral embolism (Hoobler 1942) but it has also been thought responsible in some cases for disturbances of cardiac rhythm (premature beats atrial paroxysmal tachycardia atrial flutter) due to irritation of cervical nerves.

**The scalenus anticus syndrome** consisting of localized and radiating pain in and from the upper precordial and clavicular and shoulder regions and trophic disturbances in either arm may simulate on occasion angina pectoris but it is usually readily differentiated by the longer duration of the pain and variation with a change in shoulder and arm position. It is caused by pressure of the anterior scalenus muscle or fibrous band representing rudimentary rib or middle scalenus muscle upon the subclavian artery (with reduction of pulse size and blood pressure) and lower portion of the brachial plexus. It can be relieved by surgery with section of the offending structures (Rogers 1941 Adson 1947) or by skeletal traction in selected cases (DePalma 1948).

**High altitude Aviation hazards** Climate and weather. High altitude increases the work of the heart in attempting to supply to the tissues an adequate amount of oxygen the pressure of which in the inspired air is decreased be-

cause of the decrease of atmosphere at points much elevated above sea level. The influence of high altitude depends on several factors: first the height above sea level; second the individual's capacity to compensate for the oxygen decrease; third the length of time the subject has lived at the high altitude; and fourth the degree of physical activity at this altitude. Below a height of 5 000 feet (about 1 700 meters) altitude has little or no effect; between 5 000 and 10 000 feet it probably has a slight to moderate effect; between 10 000 and 15 000 feet it has considerable effect; and over 15 000 feet (5 000 meters) it has a very marked effect on the circulation. Individuals vary greatly in their ability to adjust themselves physiologically to high altitudes and therefore in their ability to withstand *mountain sickness*, which is due to low arterial oxygen saturation; the cause of the difference is not clear, but it seems to depend in part at least on the capacity of the lungs to allow a rapid diffusion of oxygen from alveolar air to blood stream. Tests of this capacity of an individual to endure the low oxygen pressure of high altitudes either on land or in the air may be made at sea level without the expenditure of time and money necessary for traveling to very high altitudes. At an altitude of 15 000 feet the heart works about 20 per cent harder to accomplish 20 per cent less work than at sea level (Barcroft and associates 1922). An altitude of 10 000 feet is the more or less critical height above which mountain sickness is likely to occur. The more prominent symptoms of mountain sickness are headache, vertigo, nausea, dyspnea, palpitation, and weakness. The electrocardiogram of normal soldiers at 15 000 feet has shown elevation of *S T* segments and inversion of *T* waves in several precordial leads corrected by descent to sea level (Alzamora and Monge 1949).

*Aviation medicine*, which has developed of late by leaps and bounds under the stimulation of modern warfare, includes not only the effect of high altitude as in mountain sickness, which can be successfully combated by the inhalation of oxygen, but also two other important circulatory strains, namely (1) that of the centrifugal force on the blood mass resulting from intense acceleration of the speed of modern planes and from abrupt change in direction, as in dive bombing, in part at least controlled by special equipment which compresses the lower part of the body and by prone body position; and (2) that of air embolism resulting from very rapid climbs to very high altitudes, requiring control by preoxygenation and denitrogenation or by the maintenance of a more or less uniform atmospheric pressure protecting the aviator. Very few cardiac deaths, however, have been recorded among several million passengers in air travel where the hazards are relatively slight (Graybiel 1941). Of the greatest importance in the selection of pilots and other air crew is testing them for their ability to stand these various strains, since individuals vary greatly and in maintaining them in a state of physical fitness.

Individuals who have lived long at high altitudes, for example 15 000 feet or more, acquire an ability not found in the newcomer to adjust the circulation to the low oxygen pressure. The adjustment expresses itself by the development of polycythemia, barrel shaped thorax, and ability to undertake

relatively strenuous exertion which is impossible for the new arrivals. That the adjustment is not adequate is shown by the uniform occurrence of cyanosis, clubbing of the fingers and pulmonary emphysema in the case of natives of very high altitudes (Talbot and Dill 1936). The lowest oxygen saturation of arterial blood in a series of six healthy workmen resident at 17 500 feet studied by Talbot and Dill (1936) was 67.6 per cent (normal 95 per cent) while the average in the six was 75 per cent and in ten temporary residents 76.2. Removal to low altitudes or the administration of oxygen is necessary to combat the excessive anoxemia that comes with an acute pulmonary disease like pneumonia. The degree of physical activity possible at high altitudes depends on the three factors already discussed: even a native with good compensation is unable to perform at high altitudes an amount of work easily possible at low altitudes without symptoms of circulatory distress (chiefly dyspnea and tachycardia). Heart failure is rare at high altitudes unless there is already serious heart disease. An increase in heart size, especially right ventricular, in natives living at 4 540 meters has been reported by Rotta (1947).

In contrast to the effect of low oxygen tension in the inspired air, high oxygen atmospheres (up to 50 per cent of oxygen) have shown no deleterious effects in the case of 2 normal men and 28 patients with cardiac insufficiency who were kept in such atmospheres for periods of time ranging from 5 days to 7 months: the patients were almost invariably benefited by such therapy (Richards and Barach 1934). Pure oxygen at atmospheric pressure inhaled for many hours may produce pulmonary edema in animals but has been well tolerated and very helpful in human patients (A. L. Barach personal communication 1942). There has been no proof of depression of the respiratory center in the brain by prolonged inhalation of high percentage of oxygen except in rare deeply cyanosed cases with extensive pulmonary disease who require the aid of a respirator adequately to take in oxygen and to blow off carbon dioxide.

Very high atmospheric pressures may have harmful effects, as in caisson disease with its hazard of the bends, due to gaseous emboli of nitrogen in blood and tissues (Behnke 1940; Shilling 1941).

Extreme variations in weather have an important effect in cardiac patients in precipitating or increasing disorders of function such as congestive failure, coronary insufficiency (angina pectoris) and arrhythmias. Intense cold, high winds and excessive humidity are especially harmful but as yet little adequate study has been made on this important problem. In one series of cases attacks of coronary occlusion were found to be more frequent in winter than in summer (Bean and Mills 1938) but in another series in New England (White and Brasil 1935) the attacks were scattered quite uniformly throughout the months over a ten year period. Effort angina pectoris is certainly more common in cold weather but it is important incidentally to note that in intensely hot weather physical effort which might precipitate cardiac symptoms is normally reduced to a minimum.

**Work and exercise** **Athletics** Physical work and exercise do not primarily cause heart disease or heart damage except in the rarest cases (see below) though they may precipitate or aggravate symptoms and signs of heart disease already present and may temporarily exhaust the cardiovascular reserve even in a healthy individual. There has been much written about the industrial heart, the athletic heart, and the military heart, but final conclusions cannot yet be drawn from the insufficient data that we possess. Suffice it to say that all three of these so-called heart conditions are nothing more nor less in most cases than fatigue or effort syndrome, especially marked in nervous individuals in whom it may amount to neurocirculatory asthenia. In some cases there may be also hypoglycemia and in others, who perspire much, lack of sodium chloride, relieved by glucose and by common salt respectively.

Two other factors, however, are significant. One is real trauma due to exercise or work that may cause either directly or indirectly rupture of some part of the heart or great vessels, even when the heart is normal. The other is the possibility, in fact perhaps the likelihood of actual increase in muscle bulk (hypertrophy) resulting from strenuous exertion continued for years. It is very difficult to decide this matter of hypertrophy. In the first place it is very rare to obtain postmortem data in the case of vigorous athletes who, while in normal health, meet a sudden accidental death. Secondly, slight to moderate hypertrophy alone may occur during life but not be particularly obvious on examination, even by roentgen study unless dilatation is also present. Thirdly, the range of the normal heart size is so great, even in individuals of the same height, weight, and age, that we have as yet no way of knowing whether or not in many cases there has been a change, even when we determine the exact heart weight post mortem. Some more accurate correlation, probably with body build, than we possess at present is necessary, as already stated in Chapter 2, before we can draw definite conclusions. At present a very appreciable increase in size is possible in many cases without exceeding the outer normal limit. Finally, sufficient studies following the heart size of individual athletes or soldiers over many years have not yet been made. Some observations have been reported which suggest that slight enlargement of the heart is more likely to be found in professional ski runners, cyclists, and oarsmen than in other athletes. Also a few football players may have shown slight cardiac enlargement. However, even veteran marathon runners have failed to show enough hypertrophy to be evident by roentgen ray study. Cardiac enlargement, apparently largely dilatation, found in some athletes during their period of intense sport may subside when the athletic life is given up. The immediate reaction of heart size to vigorous exercise in an athlete is usually a diminution, as shown by roentgen ray study, not to be accounted for entirely by a rapid heart rate.

It appears likely from the data that we possess at present that most hearts can endure great physical strain without difficulty and without enlargement, but that a few react differently and eventually increase in size. It is quite possible that the chances of producing cardiac enlargement by physical strain

( the athletic heart ) are greatest when four factors coincide (1) great physical strain (2) rapid growth at adolescence (3) temporary or chronic ill health as from respiratory infection or anemia and (4) unfavorable myocardial inheritance (to endure such strains) In most instances however the circulatory system including the heart can in youth and sometimes even at older ages be brought to a high degree of efficiency and stamina in athlete soldier and laborer alike by prolonged and skillful training

It is of considerable interest to note that the hearts of very active animals are much larger than are those of relatively inactive animals of the same size for example the heart of the hare is three times as heavy relative to body weight as that of the rabbit while the heart of the racing greyhound is in proportion to size the largest mammalian heart of all (Herrmann 1926) Finally when animals such as dogs or rats are made to exercise strenuously for long periods of time it is found that eventually their hearts are considerably larger and heavier than those of control animals of the same age and size and even from the same litter This is especially true when the strenuous exercise is imposed during the period of rapid growth There is no indication that such hypertrophy when it does occur is harmful Recent studies indicate that athletes do not suffer early disability or death because of their exercise in youth in fact the reverse seems to be the case at least as regards oarsmen (Cooper, et al 1937 Hartley and Llewellyn 1939) An interesting volume was published by Morgan in 1873 entitled *University Oars* a critical enquiry into the after health of the men who rowed in the Oxford and Cambridge Boat Race from the year 1829 to 1869 based on the personal experience of the rowers themselves these oarsmen lived longer and healthier lives than the average Britisher of their day Although it is true that it is the man of muscle (mesomorph) and therefore the athlete who is more prone than either ectomorph (thin) or endomorph (fat) to develop serious coronary heart disease in middle age (see Chapter 21) the oarsman is as a rule not built like the usually bulky mesomorph that is he is taller and more rangy and so may be less vulnerable to early coronary atherosclerosis Much more study of all types of athletes in this respect is needed

It is possible for a well trained athlete to support a valvular lesion like aortic regurgitation if not marked, without symptoms and be much more fit physically for the time being at least than a person living a sedentary life whose heart is undamaged In fact in the absence of important symptoms exercise in moderation is beneficial for a person with chronic heart disease at any age because of its favorable effect on the peripheral circulation (reducing venous stasis and the hazard of thrombosis) pulmonary reserve general musculature digestion nervous system and morale It is wise however in the long run to limit considerably the strain of vigorous exercise on the heart when there is clear evidence of enlargement with or without valvular disease especially during rapid growth in adolescence

**Military service** The problem of the selection of recruits for military service is a matter of recurrent interest and importance What has been said above in

the last section on the effect of work and exercise on the heart and circulation (as well as in the previous section on high altitude) has a direct bearing on this subject. The other points of importance concern the incidence of cardiovascular defects found in the young men of any given community or country and the relative size of the army and navy and air force required. When relatively small forces are needed the physical standards for acceptance of the recruits can be kept at a high and rigid level with only two classifications namely fitness for full combat duty and unqualified rejection. Those accepted for service under these conditions should have no hint of suspected heart disease in the form of cardiac enlargement, murmurs of valvular defects, disturbing arrhythmias, overhigh blood pressure or pulse rate or troublesome symptoms either of cardiac origin or of neurocirculatory asthenia, nor should there have been a history of rheumatic fever, pericarditis or coronary heart disease. When however there is a large expansion of military forces the bars must be let down and not only the criteria for full combat duty made less rigid but also a third classification adopted namely of acceptance for limited service. During preparations in this country for World War II about 20 per cent of the candidates for military service were rejected for physical reasons and about 8 per cent of the rejections were for cardiovascular defects, ranking fifth in the list of causes for rejection after defects of teeth, eyes, nervous system and ears in that order. The reasons for cardiovascular rejections varied greatly in different parts of the country but on the average ranged as follows in the order of frequency: valvular disease, hypertension, neurocirculatory asthenia and tachycardia. The chief difficulties concerned the upper limits of acceptable blood pressure and pulse rate, the interpretation of a relatively slight apical systolic murmur and the detection of men likely to develop neurocirculatory asthenia under too little provocation. More studies were considered necessary to solve these problems which concerned not only fitness for service at the moment but also the future state of health after the war should end (Levy, Stroud and White, 1943). A follow up study of men rejected during World War II for cardiovascular reasons has indicated that the only important problem that remains is that of the upper limits of acceptable blood pressure (White et al., 1949).

After the recruit's admission to the armed forces his heart is likely to trouble him very little since presumably it is normal to start with. He may acquire rheumatic fever and if he does he may have to be discharged from service not so much because of any heart disease that may result (unlikely if not already present before examination as a recruit) but rather because of prolonged illness and liability to recurrence. Syphilitic aortitis with aneurysm or aortic regurgitation, once the typical soldier's heart and responsible for half of all the cardiovascular deaths in the British Army in the middle of the nineteenth century (Myers, 1870) has now been practically wiped out—only one death from aortic aneurysm occurred among 175 000 officers and men in the United States Army in 1937. Hypertension may develop among the older officers and men (Hillman, Levy, Stroud and White, 1944). The other current difficulties

of the present day seem to be neurocirculatory asthenia and the discovery by symptoms or electrocardiogram, of presenile coronary heart disease (White 1941, 1951) Coronary heart disease was diagnosed in over 800 men under the age of 40 years in the army of the U S A during World War II, half of the diagnoses were confirmed by autopsy (Yater et al, 1948 see Chapter 21)

The problem of the airman's heart and circulation is a very special one As perfect as possible at the time of selection the aviator needs chiefly to avoid staleness and to keep himself fit so that, with the aid of oxygen, he may avoid the hazards of anoxia and of centrifugal forces in flights at high altitudes at high speeds and with sudden changes in speed and in direction Various tests especially the Schneider Index (see Chapter 10), have been instituted to measure the fitness of pilots and other aviators but not one of them is apparently as reliable as the close personal daily observation of the men by their own flight surgeon (Poppen 1941)

**Pregnancy** Pregnancy augments the blood flow and it has been estimated that the work of the heart increases steadily during pregnancy to a level of about 50 per cent above that in the nonpregnant state (Stander and Cadden 1932) it used to be thought that this maximum strain was at or just prior to full term but it has since been shown that it occurs toward the end of the ninth lunar month at which time lightening takes place following which there is much less strain on the heart and hence less failure in cardiac cases in the tenth month (Cohen and Thomson 1939) Another study has indicated that an important factor increasing the blood flow and the work of the heart in the pregnant state is the placental circulation the effects of which resemble those of an arteriovenous aneurysm (Burwell et al 1938) There has been a difference of opinion as to whether or not the heart is enlarged for the time being because of this increased work or increase in blood volume In advanced pregnancy it is difficult to judge the heart size because of the upward displacement of the heart by the enlarged uterus which displacement incidentally is responsible for prominence of the Q waves and inversion of the T waves in Lead 3 of the electrocardiogram so often found during the latter half of pregnancy There probably is slight enlargement in pregnancy, but it is clear that it is not great One other general observation of circulatory interest in pregnancy is that the enlarged uterus tends to obstruct the venous return to the heart and to cause stasis in the leg veins

Studies of pregnant women in this country have shown that about four per cent of all cases have heart symptoms or signs half of these have merely functional mitral systolic murmurs (probably associated with slight functional cardiac dilatation of little or no importance) or neurocirculatory asthenia the other half (2 per cent of all cases) have organic heart disease In some places Montreal for example a lower incidence of heart disease (1 per cent) has been found (Campbell 1923) in others it has apparently been much less (Schmidt in Bonn 0.4 per cent for example) and in others somewhat more (Daly in Chicago 2.8 per cent Schaupp in San Francisco 2.7 per

cent) More recent reports have given figures of 3.02 per cent (720 out of 23,858 pregnant women—Stromme and Kuder 1946) 3.2 per cent (203 cardiac cases of 6,285 consecutive pregnancies—Lesse, 1948) and 0.8 per cent (225 among 29,713 cases—MacRae 1948) The large majority of pregnant women with real heart disease have chronic rheumatic valvular defects, mostly mitral disease with more or less stenosis. Congenital defects, syphilitic aortitis, hypertension, subacute bacterial endocarditis and thyrotoxicosis are relatively rare in pregnancy, making up altogether less than 10 per cent of the cases of heart disease in pregnancy. Of the 225 cases noted by MacRae (1948) 91.5 per cent were rheumatic, 5.8 per cent congenital and 2.7 per cent of other types.

The important question concerning heart disease in pregnancy is the prognosis, one of the most difficult problems in medicine. Many patients, even with considerable mitral stenosis, go through pregnancy, childbirth and the puerperium without any difficulty whatever and with no obvious injury to the heart, although some authorities believe that even in such cases the strain eventually tells by shortening life. This is a supposition difficult to prove because of the fact that persons with mitral stenosis usually live short lives anyway and are prone to heart accidents or failure even though not subjected to the strain of pregnancy. Some cases, even without evidence of much heart disease, do badly because of the development of atrial fibrillation, of recurrent rheumatic infection, or of unexpected heart failure during pregnancy. No rule can be set except that pregnancy should be forbidden or terminated early if symptoms and signs of heart failure appear early or if there have ever been such symptoms or signs; the same advice applies when there are complications of atrial fibrillation, free aortic regurgitation and hypertension. It is particularly these conditions—atrial fibrillation, heart failure, marked aortic regurgitation and hypertension—that have been found by experienced observers to menace the lives of both mothers and infants. Functional tests are of little or no importance in prognosis in comparison to the structural lesions that are found (Hamilton 1941). However, even such conditions as marked mitral stenosis, coronary thrombosis and heart block have not prevented normal pregnancy and delivery, although it is certainly advisable to warn such patients against pregnancy except in the very rare case of uncomplicated congenital heart block. Although the presence of heart disease of any type or severity always adds to the risk of pregnancy, the chance may often be taken and even at moderate risk it may be justifiable to allow one pregnancy to occur and to continue if there is a great desire for a child. One must remember incidentally that all the strain is not from the pregnancy and childbirth; the care of the child after birth and of the growing family may be the cause of greater strain.

Almost all the congenital cardiovascular defects have been represented among the successful cases except for those intensely cyanosed septal defects, patent ductus arteriosus and aortic coarctation, have not been a bar. Even subacute bacterial endocarditis with penicillin during pregnancy has been successfully treated with living mother and child and uneventful pregnancies



have taken place in severely hypertensive women after successful reduction of their blood pressure by thoracolumbar sympathectomy

It is of the greatest importance to follow a cardiac patient through pregnancy with conscientious care and meticulous treatment. This care has already proved invaluable and is the chief therapeutic and preventive measure. In the nineteenth century the maternal mortality of pregnant cardiacs was almost 50 per cent (Zarday 1948). Hamilton (1941) has concluded that careful following of pregnant cardiac patients at the Boston Lying In Hospital has reduced the maternal mortality from about 12 per cent to less than 3 per cent in the past twenty years. In his series of 1 000 pregnant cardiac patients, the first 500 showed a maternal mortality of 5.4 per cent and a fetal mortality of 18.0 per cent while the second 500 did considerably better with a maternal mortality of 2.6 per cent and a fetal mortality of 15.8 per cent. The maternal death rate rose to 33.3 per cent in the presence of atrial fibrillation. MacRae (1948) reported a maternal mortality of 3.1 per cent. Lesse (1948) one of 1.5 per cent and Stromme and Kuder (1946) one of 1.3 per cent.

If termination of pregnancy is essential the kind of anesthetic and type of operation (Cesarean section or delivery from below) are less important than the skill, experience, and care of the anesthetist and operator. Of a group of 74 cases of pregnancy with heart disease reported by Frey and Lardi (1978) all did well, 43 being allowed to go to term with spontaneous childbirth, 19 being operated on under local anesthesia by Cesarean section and 12 cases being interrupted early in pregnancy. This record is very unusual; generally a mortality of about 2 per cent is reported in pregnant cardiac patients. One authority (Jensen 1927) believed that the difference of opinion expressed in the literature concerning heart disease and pregnancy is due to the inconsistency of comparing massed statistics from public or large hospitals with figures from the private practice of experienced obstetricians. In general it is much better to allow patients to go to term and to deliver themselves (with help if necessary) than to interrupt pregnancy at an advanced stage. It is also best to avoid Cesarean section.

For the immediate treatment of heart failure in pregnancy the usual methods such as digitalis administration and diuretics are indicated but not termination of pregnancy at least until *after* the heart failure has been controlled. For auricular fibrillation digitalis, quinidine or both should be employed. Apparently these drugs do not affect the fetus in a harmful way.

Finally it is to be observed that the old tradition that the cardiac patient has a shorter or easier labor than the normal woman is not founded on fact (Nelson and Eades 1935).

**Anesthesia and surgical operations.** Anesthetics and operative procedures do not cause heart disease although serious poisoning of the heart may occur from the effect of chloroform and abnormalities of the heart beat are common under anesthetics during operations. Chloroform and the newer related anesthetic cyclopropane may produce premature beats, paroxysmal tachycardia and in experimental animals ventricular fibrillation and death. It is likely that

sudden death of patients during anesthesia by these agents comes in this same way, certainly they should be administered only by experts and never when the heart is already irritable or diseased. General anesthesia with ether or ethylene and oxygen and local anesthesia are the procedures of choice from the cardiovascular standpoint. During ordinary anesthesia premature beats, paroxysmal atrial tachycardia and disturbance of the sinoatrial pacemaker have been noted by electrocardiographic study to be common; they are generally only of passing interest although alarm may be occasioned temporarily by the very rapid pulse of paroxysmal tachycardia which subsides as a rule without leaving any trouble behind it and sometimes is dramatically banished by carotid sinus pressure. Very rarely a paroxysm of tachycardia may be associated with a state of shock which proves fatal; in such cases it is the very low blood pressure and not the rapid heart action that is the serious sign. Anoxemia during anesthesia may produce temporary atrioventricular block. Spinal anesthesia is usually attended by a marked drop in blood pressure; in the presence of hypertension or serious coronary heart disease spinal anesthesia should be avoided or undertaken cautiously.

Patients with heart disease of nearly all types (rheumatic, hypertensive, coronary, congenital, thyrotoxic) go through anesthesia and surgical operations surprisingly well even with atrial fibrillation, heart block or slight angina pectoris or congestive failure provided care is used. But marked congestive failure, very recent coronary thrombosis (that is, within a few weeks), severe angina pectoris, marked aortic stenosis and syphilitic aortitis add very appreciably to the operative risk, sudden death being a common ending for all of these conditions. Operations of choice, for example, herniotomy, interval appendectomy and often cholecystectomy and prostatectomy should be routinely avoided in such cases. If there is time, preoperative preparation of cardiac patients when indicated is usually helpful, such as saturation with digitalis for congestive failure or atrial fibrillation, except in rare cases; however, the presence of heart disease should not deter one from emergency operations. In the presence of thyrotoxicosis, congestive failure and atrial fibrillation may actually be cleared away by the operation itself (subtotal thyroidectomy) after suitable preparation with iodine (see Chapter 18) or by the newer use of irradiated iodine (see Chapters 21 and 30). It is also true that it is often wise to assume the risk of operation in cardiac patients for other conditions which are proving intolerable for life or comfort, for example, lumbodorsal splanchnic resection for severe hypertension in youth or middle age (see Chapter 19) and resection of the prostate gland for urinary obstruction (Mallory et al., 1943).

In thoracic surgery, routinely and when disturbing arrhythmias are present or threaten in other surgical fields, protection of the patient by the administration of quinidine sulfate orally or parenterally (e.g., 0.2 to 0.4 gm. 3 to 6 gr. every 2 to 4 hours during the necessary period of time) may prove very helpful or even lifesaving.

Collapse or death during anesthesia or surgical operation is rarely due to heart trouble; it is almost invariably the result of shock from hemorrhage.

*infection trauma, or other cause, and the treatment of such collapse should not be directed at the heart but at the condition of shock hemorrhage or infection* For cardiac standstill however, the heart should be massaged with the hand through the incised diaphragm if the abdomen is open or the thorax itself can be opened in the emergency if not already entered in the course of thoracic surgery Moreover if the heart is normal to start with epinephrine (adrenaline) chloride (solution of 1 to 1 000) may be injected within two or three minutes directly into the heart (0.25 to 0.5 cc) to restore a normal beat in some cases There have also been introduced devices to stimulate the heart to resume its beating or to abolish ventricular fibrillation by the use of electric shocks (Hyman, 1935, Beck 1941 and 1947)

Sufficient authentic recoveries by these procedures have by now (1951) been reported to make them advisable in every case of cardiac standstill during anesthesia the first method namely, that of massage is far preferable to the second since epinephrine may itself especially when applied directly to a diseased or irritable heart induce ventricular fibrillation and death The value of the massage combined with artificial respiration was demonstrated some years ago in a spectacular case of recovery at the Lahey Clinic 20 minutes after the heart had ceased its spontaneous beating (Adams and Hand 1942)

Postoperative complications may include so-called heart attacks or cardiac emergencies in particular paroxysmal tachycardia and paroxysmal atrial fibrillation and coronary thrombosis angina pectoris and acute pulmonary edema (with or without asthma) or other evidences of congestive heart failure are not common even in the presence of serious heart disease largely because the patients are having a regime of complete rest It is important when the cardiac reserve is low to avoid much saline solution by vein before or after operation since the extra sodium may precipitate pulmonary or systemic congestion with edema Procaine in 0.1 per cent solution intravenously has been helpful in dispelling bothersome ectopic tachycardia during surgical operations Disagreeable abdominal complications such as excessive intestinal gas may however precipitate heart trouble in those likely to have it More common postoperatively than serious cardiac conditions is the frequent complication of *pulmonary embolism* which may itself give rise to the acute cor pulmonale and be confused with coronary thrombosis or acute pulmonary edema of cardiac origin (see Chapter 20), it demands search for venous thrombosis in the legs and ligation of the thrombosed veins bilaterally since both legs are usually involved—this may be a lifesaving measure (see Chapter 28)

**Excessive ingestion of food and fluid and salt** *Overeating* may have so far as the heart is concerned a few untoward sequelae In the first place a state of obesity ill health and fatty infiltration of the heart may result from the excessive ingestion of food and secondly heart failure atrial fibrillation angina pectoris or acute coronary thrombosis may be precipitated by a hearty meal especially if followed at once by vigorous exertion or by horizontal recumbency This association between hearty eating and coronary thrombosis

or angina pectoris occasioned the one time erroneous diagnosis of rapidly fatal acute indigestion

*Ingestion of excessive fluids and salt (sodium)* It was long thought that the ingestion of excessive amounts of fluid daily for long periods of time might lead to cardiac enlargement and failure and the most typical example of such a state was called the beer heart. It was reasonable to believe that the increased work required of the heart to dispose of the enormously increased amount of fluid absorbed into the circulation by the copious beer drinking of former times (sometimes as much as 30 liters of beer a day were ingested routinely by champions in Munich) might lead to cardiac hypertrophy and dilatation (Bollinger 1884) however doubt was later cast on this idea by the fact that hypertension undoubtedly existed in many individuals but was unsuspected in the days before blood pressure measurements. Occasionally large hearts are still found with no other explanation than that they are beer hearts. However, evidence against the existence of the beer heart is the finding that ingestion of very large amounts of water (comparable to the volume of beer drunk by the champions of former days) by patients with diabetes insipidus does not apparently cause cardiac enlargement (Rowntree personal communication 1930)

*The immediate effect of excessive fluid and salt (sodium) ingestion or injection* is sometimes clearly seen as an injurious one in the case of a weakened heart or circulation. It is known that temporarily the blood volume may be much increased by the ingestion of an excessive amount of fluid containing salt especially if the kidneys are slow to function. In recent years when the forcing of fluids has been a common therapeutic procedure in the treatment of acute infection, and especially in the stimulation of kidney secretion and the washing out of kidneys and bladder in cases of prostatic hypertrophy before and after operation the strain on the heart and circulation of weakened patients has sometimes manifested itself by the development of dependent edema or by the precipitation of acute pulmonary edema (with or without cardiac asthma) or angina pectoris. The intravenous injection of considerable amounts of normal saline solution (500 to 1 000 cc for example) has also on occasion been the cause of accidents because of the strain on the heart. While the forcing of fluids continues rest, digitalis and other such measures may prove ineffective. It is usually a simple matter to establish a compromise between the surgeon and the physician in the matter of the amount of salt and fluid intake in a surgical patient subject to angina pectoris or congestive heart failure. Glucose solutions may helpfully replace saline on occasion. And in a cardiac patient acutely or chronically ill with congestive heart failure the one final measure that may lead to recovery temporary at least after other measures have failed is salt (sodium) restriction. (See Chapter 30 and Bibliography at end of this chapter)

*Gastrointestinal diseases and disorders* Indigestion aside from overeating which I have just discussed is related to heart disease in three ways (1) as an associated not a causative factor (2) as an irritating or aggravating factor

in the production of disorders of heart function whether the heart is normal or diseased and (3) as a cause of confusion in diagnosis. Thus it is common for *spasm of esophagus or stomach (cardiospasm or pylorospasm) hiatus (diaphragmatic) hernia of the stomach, gallbladder disease (with or without stones) irritable or sluggish colon (with constipation) and much gas in stomach and intestines* (often consisting of swallowed air—cribbing) to be present in a person who has heart disease particularly of the hypertensive or coronary type. This association is mainly an incidental one dependent primarily on two factors both common denominators namely (1) the aging process and (2) a type of individual or manner of life. That a closer association does not exist is shown for example in the case of gallstones and coronary atherosclerosis of high degree which occur together twice as commonly as separately by the following facts (1) the former, gallbladder disease is more common in women while the latter coronary heart disease is more common in men and (2) the youngest cases of either condition are uncomplicated (Walsh et al 1941). Peptic ulcer is no more often found with heart disease than without it.

The second connection between these various gastrointestinal disorders and heart trouble namely that of provocation of symptoms is an important practical problem and often demands careful study and skilful treatment. Extrasystoles paroxysmal tachycardia and even atrial fibrillation can be excited reflexly by gastrointestinal disorders even in a normal heart subsiding when the indigestion ceases. Sometimes serious disorders of function angina pectoris and congestive failure can be prevented or relieved in a cardiac patient by straightening out the digestive trouble and from the standpoint of the sufferer from indigestion gastrointestinal symptoms may be relieved by correction of disorders of the circulation. However radical measures of treatment such as cholecystectomy are not to be undertaken lightly hoping to get rid thereby of some such condition as angina pectoris. Emergency operations may be justified but a cardiac patient may be made worse with the precipitation even of myocardial infarction or death by an operation of choice or convenience.

Cirrhosis of the liver due to heart disease is uncommon. Only 35 cases were found by Garvin (1943) among 790 consecutive adult autopsied patients who died of heart disease most commonly in those who had had chronic or recurrent congestive failure secondary to rheumatic heart disease (14 of 119 cases) or to hypertensive heart disease (14 of 264 cases). In my experience the more definite cases have been those with congestion due to mitral stenosis with or without tricuspid stenosis and chronic constrictive pericarditis but it is important to note that the liver may be engorged with blood and ascites may be present in such cases for a long time before any appreciable cirrhosis of the liver develops.

Finally perhaps the most important relationship between heart trouble and indigestion is that of confusion in diagnosis often their symptoms re

semble each other closely: particularly angina pectoris and the pain of cardiospasm on the one hand and the acute symptoms of myocardial infarction and gallstone colic on the other (see Chapter 21) the skill of the physician to distinguish them may be taxed to the utmost particularly when as so often happens both conditions cause symptoms in the same person and at the same time

**Renal disease and uremia** *Acute hemorrhagic nephritis* particularly in children may be accompanied by severe myocardial involvement with cardiac dilatation and even failure, which tend to subside as the nephritis clears (Ellis 1936 Master et al 1937 Langendorf and Pick 1938 Rubin and Rapoport 1938 Whitehill Longcope and Williams 1939) this is not hypertensive heart disease

*Chronic nephritis* has no direct bearing on the heart until renal insufficiency with *uremia* and potassium poisoning develop (see section on Poisoning) Nephrosis with edema and salt losing nephritis are important conditions which may complicate or indeed simulate cardiovascular disease and of course, chronic nephritis frequently complicates though it rarely initiates hypertensive disease

**Collagen diseases and allergy** There is an interesting and puzzling group of closely related diseases which involve the collagenous (connective) tissue of the body primarily often including that of the heart and which may be due to an allergic type of reaction One of these conditions is *disseminated lupus erythematosus* (diffuse collagen disease) which has attracted much attention of late in this disease of unknown cause polyserositis with pericarditis is common and there may be also endocarditis and myocardial involvement and even congestive failure *Polyarteritis (periarteritis) nodosa* is another rare but important disease of unknown origin sometimes attended by a high count of eosinophiles in the blood which also involves the viscera including the myocardium by causing a nodular reaction in the walls of the small arteries often leading to occlusion and local necroses (see Chapter 28) In the *Libman-Sacks syndrome* attended like the other two diseases mentioned above by skin manifestations in some of the cases there has been described an atypical verrucous endocarditis In some cases of *scleroderma* myocardial changes leading to fibrosis and failure have been found In *rheumatoid arthritis* also of unknown etiology pericarditis and endocarditis and myocarditis (even with partial heart block as shown by a long P R interval) may occasionally appear as complications not to be ascribed at least in most cases to a coincident rheumatic fever In a series of 45 autopsied cases of rheumatoid arthritis studied at the Massachusetts General Hospital 45 per cent showed involvement of the pericardium 17 per cent of the myocardium 20 per cent of the endocardium and 10 per cent of the aorta probably the result of the etiologic factor behind rheumatoid arthritis itself In several cases there were nodules in the pericardium and other tissues almost pathognomonic of the disease

Also a *serum carditis* and deleterious effects of *anaphylaxis* (allergy) on the myocardium have been described. Electrocardiographic abnormalities are common in these various diseases. How much all these different conditions (even including rheumatic fever) are related in etiology and especially in their effects on the heart and blood vessels we do not yet know but there does seem to be some sort of definite relationship which is further borne out by the favorable effect on nearly all these conditions at least pro tem by the new hormonal therapy with adrenocorticotrophic hormone (ACTH) and cortisone.

**Miscellaneous conditions** Before this part of the book is concluded there are various other cardiovascular relationships which though rare unimportant or poorly understood deserve mention. Some of these were included in the long list of miscellaneous causes of minor abnormalities of the heart culled by von Bonsdorff from the records of the Boston City Hospital some years ago (1939) but there are still others of possible interest.

Associated with acute hypertension in the *toxemias of pregnancy* (eclampsia) there may be serious toxic myocardial dilatation with acute heart failure and pulmonary edema. The heart may dilate also in the severe stages of the toxic reaction to *burns* and *exfoliative dermatitis*.

*Polyserositis* of high degree and long course and of unknown etiology is associated with a good many of the cases of chronic constrictive pericarditis; a few of such cases are clearly due to tuberculosis but probably most of them are of that origin (see Chapter 27).

*Amyloid*, *sarcoid*, *xanthomatous* and *hemochromatous* myocardial lesions are uncommon but striking in their pathologic pictures. They are of obscure origin difficult to diagnose and as a rule but a part of widespread systemic diseases. *Amyloid disease* consists of the infiltration of various organs and tissues in the body, especially spleen, liver and kidney with amyloid, a glycoprotein, the product as a rule of a long-continued wasting disease such as tuberculosis, septic suppuration, syphilis, chronic arthritis, anemia, and cancer; the heart is not usually seriously affected but very rarely there may be so-called primary amyloid disease of the coronaries, myocardium and blood vessels with death from myocardial failure (Binford 1940). *Sarcoid disease* or Boeck's sarcoidosis consists of a benign lymphogranulomatosis with hard tubercles composed of epithelioid cells surrounded by lymphocytes without caseation which involve various organs in the body but especially lymphoid tissue; the etiology is unknown and the disease has often progressed extensively before it is discovered for it is usually symptomless at first; the mediastinal glands and lungs and spleen are particularly the site of the lesions; the myocardium and epicardium are sometimes involved but not as a rule to any important degree; no cure is known but recovery is not uncommon. *Xanthomatosis* consists of the infiltration of various tissues and organs of the body, including the skin and the heart itself with nodules or masses of cholesterol and cholesterol esters; it is a complication of a disturbed metabolism of cholesterol fats often hereditary and is sometimes seen in diabetes.

melitus its chief importance so far as the heart is concerned is its association with serious and early coronary arterial atheromatosis which may lead to angina pectoris coronary occlusion with myocardial infarction and cardiac death. *Hemochromatosis* may seriously involve the myocardium with deposition of iron in the muscle fibers and with resulting cardiac enlargement and failure and it may cause marked atrophy and pigmentation of the adrenal glands (Graef et al 1949).

Finally certain central and peripheral nervous diseases and abnormalities of skeletal musculature in function or in structure such as myasthenia gravis and progressive muscular dystrophy may be attended by heart muscle disease usually of mild degree while there remain a few mysterious cardiac diseases such as Fiedler's acute isolated myocarditis (see Chapter 25) and Davies endomyocardial necrosis and fibrosis (see Chapter 25).

## BIBLIOGRAPHY

### OTHER ETIOLOGIC FACTORS AND RELATIONSHIPS

#### Cardiac Neoplasms

- Brandes W W et al "Leiomyoma of the Pericardium" *Am Heart J* 1942 XXIII 4 6  
 Goldstein H I "Tumours of the Heart" *New York M J* 1922 CXV 148  
 Lymburner M M "Tumors of the Heart. Histopathological and Clinical Study" *Canal M A J* 1934 XXX 368  
 Mahaim I "Le Coelothéliome tawarten bénin. Une tumeur sui genres du noeud de Tawara avec bloc du cœur." *Cardiologia* 1942 VI 57  
 Moragues V "Cardiac Metastasis from Malignant Melanoma. Report of Four Cases." *Am Heart J* 1939 XVIII 579  
 Schnitzer M A and Bailey O T "Metastatic Tumor of the Heart. A Case Diagnosed During Life." *JAMA* 1937 CVIII 1787  
 Scott R W and Garvin C F "Tumors of the Heart and Pericardium" *Am Heart J* 1939 XVII 431  
 Shelburne S A "Primary Tumors of the Heart. With Special Reference to Certain Features Which Led to a Logical and Correct Diagnosis Before Death." *Ann Int Med* 1935 IX 340  
 Steuer L G and Higey C S "Primary Sarcoma of Pericardium." *JAMA* 1935 CV 1110  
 Thorel C "Pathologie der Kreislauforgane." *Ergebn d allg Path* 1903 IX 559 and 1907 XI 194  
 Wainwright, C W "Intracardiac Tumor Producing Signs of Valvular Heart Disease." *Bull Johns Hopkins Hosp* 1918 LXIII 187  
 Weller G L "The Clinical Aspects of Cardiac Involvement (Right Atrial Tumor) in Idiopathic Hemorrhagic Sarcoma (Kaposi's Disease)." *Ann Int Med* 1940 XIV 314  
 Wier D R and Jones B C Jr "Primary Sarcoma of the Heart." *Am Heart J* 1941 XXII 556  
 Yater W H "Tumors of the Heart and Pericardium." *Arch Int Med* 1931 XLVIII 627

#### Recent References (1944-1950)

- Hallhuber M L and Kasperer J M "Über ein Endothelsarkom am Vorhof des linken Herzens." *Cardiologia* 1948 XIII 305  
 Hochberg L A and Robinson A E "Primary Tumor of the Pericardium Involving the Myocardium. Surgical Removal." *Circulation* 1950 I 805



- Leffkovits A M. Neoplastic Metastasis to the Heart *Am Heart J* 1948 XXXVI 610
- McCandless F II and Faloon W W "The Diagnosis of Metastatic Tumor by Cytological Examination of the Pericardial Fluid: Report of a Case Using Shorr's Stain" *Ann Int Med* 1948 XXIX 1157
- Mahaim I *Les Tumeurs et les Polypes du Cœur Étude Anatomique Clinique* F Roth et Cie Lausanne Masson et Cie Paris 1945
- Nencki L. Primary Tumors of Large Trunks of Vessels. Report of 1 Case of Primary Sarcoma of Abdominal Aorta *Cardiologia* 1946 X 1
- Piotto A. Die Herztumoren 30 Fälle von Tumormetastasen in Herzen *Cardiologia* 1949 XIV 129
- Prichard R W "Tumors of the Heart. Review of the Subject and Report of One Hundred and Fifty Cases" *Arch Path* 1951 LI 98
- Raven R W "Secondary Malignant Disease of the Heart" *Brit J Cancer* 1948 II 1
- Ritz N D "Diffuse Melanosis Pericardial Effusion and Melanuria Associated with Malignant Melanoma. Case Report with Autopsy Findings" *Ann Int Med* 1949 XXX 184
- Shelburne P A. Primary Sarcoma of the Heart with Report of a Case. *Ann Int Med* 1948 XXIX 1139
- Walker R H. Primary Sarcoma of the Heart. A Case Report. *U S Naval M Bull* 1949 XLIX 878

### Poisoning Other Than by Infections

- Bland E F and White P D "The Strength of Digitalis in Clinical Use. A Warning" *JAMA* 1941 CXVII 1243
- Brown C E and McNamara D. Acute Interstitial Myocarditis Following Administration of Arspenamines. *Arch Dermat & Syph* 1940 XLII 312
- Cabor R C "The Relation of Alcohol to Arteriosclerosis" *JAMA* 1904 XLIII 774
- Clarke N E "The Action of Calcium on the Human Electrocardiogram" *Am Heart J* 1941 XXII 367
- Einthoven W and Wieringa J II. Ungleichartige Vaguswirkungen auf das Herz, elektrokardiographisch untersucht (Concerning the action of morphine) *Pflüger's Arch f d ges Physiol* 1912 CXLIX 48
- Finch C A and Marchand J F "Cardiac Arrest by Action of Potassium" *Am J M Sc* 1943 CCVI 507
- Graybiel A Starr R S and White P D. Electrocardiographic (and Blood Pressure) Changes Following the Inhalation of Tobacco Smoke. *Am Heart J* 1938 XV 89
- Grunewald M. Die gewerbliche Kohlenoxydvergiftung und ihre Verhütung" *Monatsschrift für Unfall Heilkunde* 1926 XXXIII 34
- Gasvergiftung in Autogaragen *Ztschr Gewerbehyg* 1927 XXXIII 55
- Hafkesbrung R et al "The Effects of Various Sulfonamide Drugs on the Electrocardiogram of the Dog" *Am Heart J* 1943 XXVI 333
- Hanzlik P J. Jan Evangelista Purkyně (Purkinje) on Disturbances of the Vision by Digitalis One Hundred Years Ago. *JAMA* 1925 LXXXIV 2024
- Hartwell A S et al "The Effect of Exercise and of Four Commonly Used Drugs on the Normal Human Electrocardiogram with Particular Reference to T Wave Changes" *J Clin Investigation* 1942 XXI 409
- Hyman A S "The Heart in Mushroom Poisoning" *Bull Johns Hopkins Hosp* 1978 XLII 8
- Jeckeln E "Über Leuchtgasschädigung des menschlichen Herzens" *Verhandl deutsch path Gesellsch* 1935 XXVIII 275
- Keith N M Osterberg A E and Burchell H H "Some Effects of Potassium Salts in Man" *Ann Int Med* 1942 XVI 879
- La Due J S. Myocardial Necrosis and Fibrosis Resulting from Administration of Massive Doses of Cardiac Glycoside" *J Pharmacol & Exper Therap* 1947 LXXVI 1
- Leary T "The Therapeutic Value of Alcohol with Special Consideration of the Relations of Alcohol to Cholesterol and Thus to Diabetes to Arteriosclerosis and to Gall Stones" *New England J Med* 1931 CCV 231

Luten D "Studies of Digitalis II Toxic Rhythms with Special Reference to the Similarity Between Such Rhythms in Man and in the Cat." *Arch Int Med* 1925 XXXV 74

Pearl R. "Tobacco Smoking and Longevity" *Science* 1938 LXXXVII 216

Thomson W A R. "The Effect of Potassium on the Heart in Man." *Brit Heart J* 1939 I, 269

Weatherby J H "Skin Temperature Changes Caused by Smoking and Other Sympathomimetic Stimuli." *Am Heart J* 1942 XXIV 17

Wolff L., and White F D "Auricular Standstill During Quinidine Sulphate Therapy" *Heart* 1929 XIV 295

Zondek H "Herzbeefunde bei Leuchtgasvergiftung II Mitteilung" *Deutsch med Wchnschr* 1920 XLVI 235

#### Recent References (1944-1950)

Almgren S Om hjartforangdringar vid kolotid (gengas) forgiftning *Nord med* 1946 XXX 938

Bellet S Steiger W A Nadler C S and Gates P C "Electrocardiographic Patterns in Hypopotassemia Observations on 79 Patients" *Am J Med Sc* 1950 CCXIX 542

Boyle M N Wegria R Cathcart R T Nickerson J L and Levy R L Effects of Intravenous Injection of Nicotine on the Circulation" *Am Heart J* 1947 XXXIV 65

Casolo "L'elettrocardiogramma nell'avvelenamento accidentale acuto de ossido di carbonio" *L'Ospedale Maggiore Milan* 1947 XXXV 47

Caloria J and Sloer M "Acute Poisoning and Cardiac Disturbances Caused by Scorpions Bite" *Rev Soc Ped del Litoral* 1948 XIII 1

Dack, S and Molosnuk, R E Cardiac Manifestations of Total Action of Emetine Hydrochloride in Amebic Dysentery" *Arch Int Med* 1947 LXXIX 228

Datke R A and Nathan D A "Electrocardiographic Changes Resulting from Phosphorus Poisoning" *Am Heart J* 1946 XXVI 98

Ehrlich, W E Bellet, S and Lewey F H "Cardiac Changes from Carbon Monoxide Poisoning" *Am J Med Sc* 1944 CCVIII 511

Finch C A Sawyer C G and Flynn J M "Clinical Syndrome of Potassium Intoxication" *Am J Med* 1946 I 337

Freund E "Elektrokardiographische Beobachtungen bei Pantherpflanzvergiftungen" *Arch hche Wchnschr* 1949 IV 550

Garcia Carrillo E "The Cardiac Action of Central American Snake Venom" *Am Heart J* 1947 XXXIII 709

Greenfield J and Gray I Lead Poisoning IX. The Failure of Lead Poisoning to Affect the Heart and Blood Vessels" *Am Heart J* 1950 XXXIX, 430

Keith N M and Burchell H II "Clinical Intoxication with Potassium Its Occurrence in Severe Renal Insufficiency" *Am J Med Sc* 1949 CCXVII 1

Kent L and Kingsland R C Effects of Emetine Hydrochloride on the Electrocardiogram in Man." *Am Heart J* 1950 XXXIX 576

Kirkegaard A., and Nørregaard S "Electrocardiogram in Severe Acute Barbiturate Intoxication" *Nord med* 1950 XLIV 1954

Krasnoff S O and Bernstein M "Acetylsalicylic Acid Poisoning with a Report of a Fatal Case" *JAMA* 1947 CXXXV 712

Levine H II et al "Advanced Disturbances of the Cardiac Mechanism in Potassium Intoxication in Man" *Circulation* 1951 III 889

Levy R L Mathers J A L Mueller A A and Nickerson J L "Effects of Smoking Cigaretts on the Heart in Normal Persons and in Cardiac Patients" *JAMA* 1947 CXXXV 417

Lilienfeld A Hochstein E and Weiss W "Aortic Myocarditis with Bundle Branch Block Due to Sulfonamide Sensitivity" *Circulation* 1950 I 1060

Mayer G., and Lévy A "Manifestations cardiaques au cours des accidents dus aux sulfamides" *Arch d mal d coeur* 1950 XLIII 525

Roth G M McDonald J B and Sheard C "The Effect of Smoking Cigaretts and of Intravenous Administration of Nicotine on the Electrocardiogram." *JAMA* 1944 CXXV 761

- Roth G M and Sheard C "The Effect of Smoking on the Vasodilatation Produced by the Oral Administration of 95 Per Cent Ethyl Alcohol or a Substantial Meal" *Am Heart J* 1947 XXXIII 654
- Suárez R M Stevenson D and Hernández Morales F "Electrocardiographic Changes During Anthelmintic Treatment of Schistosomiasis" *Am Heart J* 1948 XXXVI 973
- Tarail R "Relation of Abnormalities in Concentration of Serum Potassium to Electrocardiographic Disturbances" *Am J Med* 1948 V 828
- Tarr L "Effect of the Antimony Compounds Fuadin and Tartar Emetic on the Electrocardiogram of Man A Study of the Changes Encountered in 141 Patients Treated for Schistosomiasis" *Ann Int Med* 1947 XXVII 970

### Disorders of Nutrition Obesity

- Aalsmeer W C and Wenckebach K F "Herz und Kreislauf bei der Beriberi Krankheit" *Wien Arch f inn Med* 1929 XVI 193
- Behnke A R Jr Feen B G and Welham W C "The Specific Gravity of Healthy Men Body Weight — Volume as an Index of Obesity" *JAMA* 1942 CXVIII 495
- Goodhart R and Jolliffe N "The Role of Nutritional Deficiencies in the Production of Cardiovascular Disturbances in the Alcohol Addict" *Am Heart J* 1938 XV 569
- Hashimoto H "Acute Pernicious Form of Beriberi and Its Treatment by Intravenous Administration of Vitamin B with Especial Reference to Electrocardiographic Changes" *Am Heart J* 1937 XIII 580
- Levine E "Modern Aspects of Nutrition The Pathology of Malnutrition 21 The Relation of Faulty Nutrition to Heart Disease" *Nebraska State M J* 1927 XII 134
- McGinn S and White P D "Epicardial Fat Its Nonrecognition a Common Cause of Error in X ray Measurement of Heart Size" *JAMA* 1936 CVII 200
- Mainzer F and Krause M "The Electrocardiogram in Pellagra" *Brit Heart J* 1940 II 85
- Meixner K "Die Erweiterung der linken Herzkammer bei Rachitis" *Wien klin Wchnschr* 1928 XLI 1273
- Waring J I "Beriberi in Infants" *Am J Dis Child* 1929 XXXVIII 52
- "Nutritional Heart Disease in Children" *Am J Dis Child* 1938 LV 750
- Weiss S and Wilkins R W "The Nature of the Cardiovascular Disturbances in Nutritional Deficiency States (Beriberi)" *Ann Int Med* 1937 XI 104

### Recent References (1944-1950)

- Aalsmeer W C "Cardiovascular Symptoms of Beriberi" *Documenta Neerlandica et Indonesica de Morbis Tropicis* 1951 III
- Berkman J M "A Concept of Starvation Edema" *Proc Staff Meet Mayo Clinic* 1950 XXV 265
- Blankenhorn M A Vilter C F Scheinker I M and Austin H B "Beriberi Heart Disease" *JAMA* 1946 CXXXI 717
- Burwell C S, and Dexter L "Beriberi Heart Disease" *Tr A Am Physicians* 1947 LX 59
- Ellis L B "Electrocardiographic Abnormalities in Severe Malnutrition" *Brit Heart J* 1946 VIII 53
- Keys A "Cardiovascular Effects of Undernutrition and Starvation" *Mod Concepts Cardiovas Dis* 1948 XVII No 9
- Keys A et al "The Biology of Human Starvation" University of Minnesota Press Minneapolis 1950
- Mainzer F "The Pellagra Electrocardiogram and Its Significance" *Acta med scand* 1948 CXXXI 269
- Olson R E Pearson O H Miller O N and Stare F J "The Effect of Vitamin Deficiencies Upon the Metabolism of Cardiac Muscle in Vitro I The Effect of Thiamine Deficiency in Rats and Ducks" *J Biol Chem* 1948 CLXXV, 489
- Rachmilewitz M and Braun K "The Presence of Electrocardiographic Changes in Nicotinic Acid Deficiency and Their Elimination by Nicotinic Acid" *Am Heart J* 1944 XXVII 203

## Blood Diseases

- Cabot R. C. and Richardson O "Cardiac Hypertrophy in Pernicious Anemia" *J.A.M.A.* 1919 LXXII 991
- Elliot A H "Anemia as Cause of Angina Pectoris in Presence of Healthy Coronary Arteries and Aorta Report of Case" *Am J M Sc* 1934 CLXXXVII 185
- Ellis L H and Faulkner J M "The Heart in Anemia" *New England J Med* 1939 CCXX 943
- Gunewardene H. O *Heart Disease in the Tropics* Butterworth and Co Ltd Calcutta 1935
- Klinefelter H F "The Heart in Sickle Cell Anemia" *Am J M Sc* 1942 CCIII 34
- Norman, T L and Allen E V "The Vascular Complications of Polycythemia" *Am Heart J* 1937 XIII 457
- Porter W H "Heart Changes and Physiological Adjustments in Hookworm Anemia" *Am Heart J* 1937 XIII 550
- Szelely P "Electrocardiographic Findings in Anemia" *Brit Heart J* 1940 II 1
- Tung C L et al "The Heart in Severe Anemia" *Chinese M J* 1937 LII 479

## Recent References (1944-1950)

- Blumgart H L and Altschule M D "Clinical Significance of Cardiac and Respiratory Adjustments in Chronic Anemia. *Blood* 1948 III 329
- Gibson Q H and Harrison, D C "Familial Idiopathic Methemoglobinemia Five Cases in One Family" *Lancet* 1947 II 941
- Winsor T and Burch, G E "The Electrocardiogram and Cardiac State in Active Sickle Cell Anemia. *Am Heart J* 1945 XXIX 685

## Trauma

- Adam A. "Über die traumatischen Veränderungen gesunder Klappen des Herzens" *Ztschr f Kreislauff* 1927 XIX, 313
- Barie E "Recherches cliniques et experimentales sur les ruptures valvulaires du coeur" *Rev d med* 1881 I 132 309 482
- Barnes W P "Case of Traumatic Laceration of Inferior Vena Cava with Recovery" *Virginia M Monthly* 1938 LXV 285
- Beck C S "Wounds of the Heart. The Technique of Suture" *Arch Surg* 1926 XIII 205
- Bigger I A "Heart Wounds Report of Seventeen Patients Operated on in the Medical College of Virginia Hospitals and Discussion of Treatment and Prognosis" *J Thoracic Surg* 1939 VIII 239
- Blalock A "Successful Suture of a Wound of the Ascending Aorta. *J.A.M.A.* 1934 CIII, 1617
- Boeckel "Amputation de cuisse par gangrène consecutive à l'obliteration de l'artere femorale par une balle précédemment vue dans le coeur: présentation du blessé" *Lyon med* 1917 CXXVI 567
- Bright E F and Beck, C S "Nonpenetrating Wounds of the Heart. A Clinical and Experimental Study" *Am Heart J* 1935 X 293
- Butterworth J S and Poindexter C A "An Electrocardiographic Study of the Effects of Boxing" *Am Heart J* 1942 XXIII 59
- Clark W I "Effects of Accidents on Cardiac Employees" *Am Heart J* 1928 III 539
- Coffen T H, Rush H P and Miller R F "Traumatic Complete Heart Block of Eighteen Years Duration with Review of Literature" *Northwest Med* 1941 XL, 195
- Copeland G G "Traumatic Rupture of the Healthy Aorta without External Signs of the Cause of Death" *J.A.M.A.* 1914 LXIII 1950
- Elkin D C "The Diagnosis and Treatment of Wounds of the Heart. A Review of Twenty-two Cases" *J.A.M.A.* 1938 CXI, 1750
- Erdheim J "Medionecrosis aortae idiopathica" *Vrch Arch f path Anat* 1909 CCLXXIII 454
- Goldberger H A and Clark H E "Migration of Needle into Heart Through Chest Wall Surgical Removal Electrocardiographic and Roentgenographic Studies" *J.A.M.A.* 1935 CV 193

- Hartman F W Bolliger A Doub H P and Smith F J Heart Lesions Produced by the Deep X ray *Bull Johns Hopkins Hosp* 1927 XLI 36
- Kahn M H and Kahn S Cardiovascular Lesions Following Injury to the Chest *Ann Int Med* 1929 II 1013
- Kissane R W Koons R A and Fidler R S Traumatic Rupture of a Normal Aortic Valve " *Am Heart J* 1936 XII 231
- Koeppen S Die organische Angina Pectoris Electrica " *Munch med Wchnschr* 1940 LXXXVII 1289
- LaRoque G P Penetrating Bullet Wound of Thoracic Aorta Followed by Lodgement of the Bullet in the Femoral Artery *Ann Surg* 1926 LXXXIII 827
- LeFort R Extraction d'un élat d'obus de l'oreillette gauche *Acad de med* Oct 3 1917
- Rajasingham A S A Case of Massive Haemopericardium with Recovery after Paracentesis *Brit Heart J* 1939 I 181
- Schlomka G and Schmutz M Experimentelle Untersuchungen über den Einfluss stumpfer Brustkorbtraumen auf das Herz III *Ztschr d ges exper Med* 1939 LXXXV 171
- Shapiro S Passage of a Hollow Needle into the Venous Stream to the Heart Through the Cardiac Wall and into the Thorax *Am Heart J* 1941 XXII 835
- Streit M Elektrokardiographische Untersuchungen bei der Elektroschockbehandlung der Schizophrenie *Arch f Kreislauff* 1941 IX 11
- Warburg E *Subacute and Chronic Pericardial and Myocardial Lesions Due to Non Penetrating Traumatic Injuries* Levin & Munksgaard Copenhagen and Oxford University Press London 1938
- Warren S Effects of Radiation on the Cardiovascular System *Arch Path* 1947 XXXIV 1070

#### Recent References (1944-1950)

- Bland E F Foreign Bodies in and about the Heart *Am Heart J* 1944 XXVII 588
- DeBakey M E and Simeone F A Battle Injuries of the Arteries in World War II *Bull U S Army M Dept* 1946 V 295
- De Mattes F Su alcuni casi di danno miocardico traumatico da forza ottusa e da sforzo (commotio-contusio cordis infarto) *Minerva Medica Turin* 1949 II 445
- Elkin D C Wounds of Heart *Ann Surg* 1944 CXX 817
- Harken D E and Zoll P M Foreign Bodies in and in Relation to the Thoracic Blood Vessels and Heart " *Am Heart J* 1946 XXXII 1
- Hejtmancik M R Bankhead A J and Herrmann G R Electrocardiographic Changes Following Electroschock Therapy in Curarized Patients *Am Heart J* 1949 XXXVII 790
- Johl E and Greenstein J Fatal Coronary Sclerosis in a Boy of Ten Years *Lancet* 1944 II 659
- Kulka W Delayed Death Following Contusion of the Heart Report of a Case " *Am Heart J* 1949 XXXVIII 438
- McDonald J H and Campbell W A Traumatic Rupture of the Normal Aorta in Young Adults *Am Heart J* 1945 XXX 321
- Miller J M Rupture of the Heart from Blast Injury *Arch Path* 1947 LIII 406
- Plice S G and Pfister C W "An Electrocardiographic Study of Psychiatric Patients Before and After Electroschock Therapy" *Am Heart J* 1950 XL 257
- Sprague H H The Effect of Trauma and Strain on the Production and Aggravation of Heart Disease " *Bull New York Acad Med* 1947 XXIII 631
- White P D and Smith H W "Scientific Proof in Respect to Injuries of the Heart. *North Carolina Law Rev* 1946 XXIV 107

#### Thoracic and Spinal Deformities

- Chapman E M Dill B B and Graybiel A "The Decrease in Functional Capacity of the Lungs and Heart Resulting from Deformities of the Chest. *Pulmonocardiac Failure* *Medicine* 1939 XVIII 167
- Eden K C Vascular Complications of Cervical Ribs and First Thoracic Rib Abnormalities " *Brit J Surg* 1939 XXVII 111

- Hoobler S W "The Syndrome of Cervical Rib with Subclavian Arterial Thrombosis and Hemiplegia Due to Cerebral Embolism" *New England J Med* 1942 CCXXVI 942
- Lam C R., and McClure R D "Decompression of Heart in Severe Scoliosis Report of Case" *J Thoracic Surg* 1943 XII 517
- O'Shaughnessy L. "Cardiac Decompression by Mobilization of Chest Wall" *Lancet* 1940 I 61
- Rogers L "Cervical Ribs and Scalenus Syndrome" *Rev d Cir d Buenos Aires* 1941 XX 541
- Rosler H "Zur rontgenologischen Beurteilung des Herzgefäßbildes bei Thorax-deformitäten ([Kypho] Skoliose reine Kyphose Trichterbrust)" *Deutsch Arch f klin Med* 1929 CLXIV 365
- Sauerbruch F "Operative Beseitigung der angeborenen Trichterbrust" *Deutsch Ztschr f Chir* 1931 CCXXXIV 760
- Spurling R G and Bradford K. F "Scalenus Neurocirculatory Compression" *Ann Surg* 1938 CVII 708
- Telford E H and Stopford J S H "Vascular Complications of Cervical Rib" *Brit J Surg* 1931 XVIII, 557
- Traube L "Ein Fall von Dilatation und Hypertrophie des rechten Ventrikels bei einem mit hochgradiger Skoliose und Verbildung des Brustkorbes behafteten Individuum" *Ges Beitr z Path u Physiol* 1878 III 354

#### Recent References (1944-1950)

- Adorno A and White P D "Electrocardiographic Study of Deformity of the Chest" *Am Heart J* 1945 XXIX 440
- Adson A W "Surgical Treatment for Symptoms Produced by Cervical Ribs and Scalenus Anticus Muscle" *Surg Gynec and Obst* 1947 LXXXV 687
- De Palma A F "Scalenus Anticus Syndrome Treated by Surgery and Skeletal Traction" *Am J Surg* 1948 LXXVI 274
- Master A M and Stone J "The Heart in Funnel Shaped and Flat Chests" *Am J M Sc* 1949 CCXVII 392
- Sweet R H "Pectus Excavatum Report of Two Cases Successfully Operated on" *Ann Surg* 1944 LXIX 922

#### High Altitude Aviation Hazards. Climate and Weather

- Barcroft I and associates "Observations upon the Effect of High Altitude on the Physiological Processes of the Human Body Carried Out in the Peruvian Andes Chiefly at Cerro de Pasco" *Phil Tr Roy Soc London* 1942 Series B CCXI 351
- Bean W H and Mills C A "Coronary Occlusion Heart Failure and Environmental Temperatures" *Am Heart J* 1938 XVI 701
- Behnke A H "High Atmospheric Pressures Physiological Effects of Increased and Decreased Pressure Application of These Findings to Clinical Medicine" *Ann Int Med* 1940 XIII 2717
- Dill H B "The Effects of Physical Strain and High Altitude on the Heart and Circulation" *Am Heart J* 1942 XXIII 441
- Graybiel A "Consideration of Effects of Oxygen Lack on Cardiovascular System from Viewpoint of Aviation with Analysis of Deaths Occurring Aloft on Commercial Aircraft" *J Aviation Med* 1941 XII 183
- Monge C et al *Estudios Fisiologicos sobre el hombre de los Andes* Facultad de Medicina Lima 1938
- Richards D W Jr and Barach A L "Prolonged Residence in High Oxygen Atmospheres Effects on Normal Individuals and on Patients with Chronic Cardiac and Pulmonary Insufficiency" *Quart J Med* 1934 III 437
- Shilling, C W "Compressed Air Illness (Carsson Disease)" *US Naval M Bull* 1941 XXXIX 339
- Talbott J H and Dill H B "Clinical Observations at High Altitude Observations on Six Healthy Persons Living at 17 500 Feet and Report of One Case of Chronic Mountain Sickness" *Am J M Sc* 1936 CXCII 66

- White P D., and Brasil A "The Relationship of the Weather in New England to Certain Cardiac Conditions A Study of Patients Seen in Practice During the Past Ten Years" *Tr Am Clin & Climatol A* 1935 LI 61
- Wiggers C J "Cardiac Adaptation in Acute Progressive Anoxia" *Ann Int Med* 1940 XIV 1237

#### Recent References (1944-1950)

- Alzamora H and Monge M C "Some Observations on the Human Electrocardiogram Following Changes of Altitude Environment" *Am Heart J* 1949 XXXVII 670
- Graybiel A Patterson J L Jr and Houston C S "The Changes in Heart Size in Man During Partial Acclimatization to Simulated High Altitudes" *Circulation* 1950 I 991
- May S H "Air Travel and the Cardiac Patient An Analysis of Relevant Experimental and Empirical Data" *Am Heart J* 1950 XL 363
- Mendoza F "Transporte de cardiacos por aire" *Revista de Investigación Clínica México* 1949 I 85
- Murnaghan D P "Some Observations on the Cardiovascular Examination for Aircrew Fitness" *Am Heart J* 1944 XXVII 550
- Rotta A "Physiologic Condition of the Heart in the Natives of High Altitudes" *Am Heart J* 1947 XXXIII 669

#### Work and Exercise Athletics Military Service

- Bock A V and Dill D B *The Physiology of Muscular Exercise* (by the late F A Bainbridge) 3rd ed Longmans Green and Company London 1931
- Cooper E L O'Sullivan J and Hughes E "Athletics and the Heart Electrocardiographic and Radiologic Study of Response to Healthy and Diseased Heart to Exercise" *M J Australia* 1937 I 569
- Cureton T A "The Hearts of Athletes" *Illinois M J* 1951 XCIX 143
- Deutsch F and Kauf E *Heart and Athletics* Clinical Researches upon the Influence of Athletics upon the Heart. (Translated into English by L. M. Warfield) C V Mosby Co St Louis 1927
- Gordon B "The Effect of Effort on the Size of the Heart Observations on Animals and Marathon Runners" *Am J Roentgenol* 1925 XIV 424
- Hartley P H S and Llewellyn G F "Longevity of Oarsmen Study of Those Who Rowed in the Oxford and Cambridge Boat Races from 1829 to 1928" *Brit M Jour* 1939 I 657
- Herrmann G R "The Heart of the Racing Greyhound Hypertrophy of the Heart" *Proc Soc Exper Biol & Med* 1976 XXIII 856
- Johnson R E Brouha L and Darling H C "A Test for Physical Fitness for Strenuous Exertion" *Rev Canad de Biol* 1942 I 491
- Jokl E and Suzman M M "Aortic Regurgitation and Mitral Stenosis in a Marathon Runner with Special Reference to the Effects of Valvular Heart Disease on Physical Efficiency" *JAMA* 1940 CXIV 467
- Keys A and Friedell H L "Size and Stroke of the Heart in Young Men in Relation to Athletic Activity" *Science* 1938 LXXXVIII 456
- Kirch E and Nurnberger G "Entwicklungsgang und Ruckbildung der sportlicher Herzhypertrophie im Tierversuch" *Arch f Kreislauff* 1939 IV 1
- Koeplin F "Zur Morphologie und Funktion des Sportherzens" *Schweiz med Wschr* 1950 LXXX 1053 and 1076
- Morgan J E *University Oars Being a Critical Inquiry into the After Health of the Men Who Rowed in the Oxford and Cambridge Boat Race from the Year 1829 to 1869 Based on the Personal Experience of the Rowers Themselves* Macmillan & Co Ltd London 1873
- Nylin G "Investigations on the Blood Circulations of Gunder Hagg and Arne Andersson" *Cardiologia* 1945 IX 313
- Schneider H C and Crampton, C B "Comparison of Some Respiratory and Circulatory Reactions in Athletes and Non athletes" *Am J Physiol* 1940 CXXIX 165
- Wilce J W "The Range of the Normal Heart in Athletes" *Am Heart J* 1943 XXV 613

- Military Service (see also references under Trauma Disorders of Nutrition and Work and Exercise and in Chapter 22 Neurocirculatory Asthenia)
- Levy R L Stroud W D and White P D Report of the ReExamination of 4 994 Men Disqualified for General Military Service Because of the Diagnosis of Cardiovascular Defects *JAMA* 1943 CXXIII 937 1029 and *Am Heart J* 1944 XXVII 435
- Lewis T *The Soldier's Heart and the Effort Syndrome* Paul B Hoeber Inc New York 1919 2nd ed Shaw & Sons London 1940
- Myers A B R *On the Etiology and Prevalence of Diseases of the Heart Among Soldiers* J Churchill & Sons London 1870
- Parkinson J Cardiac Examination in Wartime *Br M J* 1940 I 428
- Poppen J R "The Cardiovascular Aspects of Aviation Medicine" *New England J Med* 1941 CCXXV 892
- Rowntree L G McGill K H and Edwards T I Causes of Rejection and the Incidence of Defects Among 18 and 19 Year Old Selective Service Registrants *JAMA* 1943 CXXIII 181
- War Department U S A Standards of Physical Examination During Mobilization Section XIV Heart Blood Vessels and Circulation *Mobilization Regulations* Washington 1940 new edition 1942
- White P D "The Soldier and His Heart" *War Med* 1941 I 158

#### Recent References (1944-1950)

- Hillman C C Levy R L Stroud W D and White P D "Studies of Blood Pressure in Army Officers Observations Based on an Analysis of the Medical Records of 22 741 Officers of the United States Army" *JAMA* 1944 CXXV 699
- Levy R L White P D Stroud W D and Hillman C C Transient Hypertension The Relative Prognostic Importance of Various Systolic and Diastolic Levels *JAMA* 1945 XXVIII 1059
- "Transient Tachycardia Prognostic Significance Alone and in Association with Transient Hypertension" *Ibid* XXIX 585
- Overweight Its Prognostic Significance in Relation to Hypertension and Cardiovascular Renal Diseases *Ibid* CXXXI 951
- Sustained Hypertension Predisposing Factors and Causes of Disability and Death *Ibid* 1947 CXXXV 77
- Traum A H and Wilcox B B Cardiovascular Disease Among Veterans of World War II *New England J Med* 1946 CCXXXIV 82
- White P D Coronary Heart Disease in Midcentury With a Note Concerning Its Military Importance *US Armed Forces Med J* 1951 II 357
- White P D Levy R L Kerr W J Stroud W D and Fenn G K Cardiovascular Rejectees A Follow up Study *JAMA* 1949 CXXXIX 1049
- Yater W M et al "Coronary Artery Disease in Men Eighteen to Thirty Nine Years of Age" *Am Heart J* 1948 334 481 and 683

#### Pregnancy

- Bernstein M Heart Block and Pregnancy Report of a Successful Delivery *JAMA* 1936 CVI 53
- Breed W B and White P D Heart Disease in Pregnancy *Boston M and S J* 1913 CLXXXVIII 984
- Burwell C S Strayhorn W D et al Circulation During Pregnancy" *Arch Int Med* 1938 LXII 979
- Campbell D B Pregnancy and Heart Disease" *Canad M A J* 1923 XIII 244
- Cohen M E and Thomson K J Studies on the Circulation in Pregnancy Summary of Studies of the Physiology of the Circulation of Normal Pregnant Women *JAMA* 1939 CXII 1556
- Daly F A "The Heart in Pregnancy" *JAMA* 1914 LXXXII 1439
- Dressler W "Schwangerschaft und Herzblock" *Wien Arch f inn Med* 1927 XIV 11
- Frey E and Lardi F "Herzfehler und Schwangerschaft und die abdominale Schnittenbindung in Lokalanästhesie bei Herzfehler" *Ztschr f Geburtsh u Gynakol* 1908 XCIII 1



- Hamilton B E and Thomson K J *The Heart in Pregnancy and the Child bearing Age* Little Brown & Co Boston, 1941
- Jensen J "Investigations on the Influence of Pregnancy and Parturition on Organic Cardiac Disease" *Acta obst et gyn scand* 1927 VI 239
- The Heart in Pregnancy* C V Mosby Co St. Louis 1938
- Mackenzie J *Heart Disease and Pregnancy* Oxford Medical Publications Henry Frowde Hodder and Stoughton London 1921
- Nelson H E and Fades M F "Some Obstetrical Aspects of Cardiac Disease Complicated by Pregnancy" *New England J Med* 1935 CCXIII 1057
- Schaupp K. L. "Cardiac Decompensation During Pregnancy and Labor" *California State J Med* 1923 XXI 290
- Schmidt, H R. "Zur Bewertung der Herzfehler in der Schwangerschaft" *Monatsschr f Geburtsh u Gynakol* 1923 LXIV 279
- Stander H J and Cadden J F "Cardiac Output in Pregnant Women" *Am J Obst & Gynec* 1932 XXIV 13

#### Recent References (1944-1950)

- Barber M D and Daley D "Coarctation of Aorta in Association with Pregnancy. Review of Literature with Description of Case" *J Obst & Gynaec Brit Emp* 1947 LIV 91
- Correll H L., and Rosenbaum F F "Multiple Pregnancies in Patients with Rheumatic or Congenital Heart Disease" *Am Heart J* 1950 XXXIX, 283
- Dillon W F and Schmitz, H E "Elevated Blood Pressure in Pregnancy A Report of 1800 Cases" *Am J Obst & Gynec* 1947 LIV 948
- Hamilton H E "Rheumatic Heart Disease in Pregnancy" *Bull New England M Center* 1946 VIII 262
- Lesse S "The Prognosis of the Cardiac Patient in Pregnancy" *Am J Obst & Gynec* 1948 LVI 477
- MacRae D J "Heart Disease in Pregnancy" *J Obst & Gynaec Brit Emp* 1948 LV 184
- Mowbray R "Heart Block and Pregnancy A Review" *J Obst & Gynaec Brit Emp* 1948 LV 432
- Stromme W B., and Kuder L. "Heart Disease in Pregnancy" *Am J Obst & Gynec* 1946 XLI 264
- Szekely P and Snarth L "The Heart in Toxaemia of Pregnancy" *Brit Heart J* 1948 IX 128
- Zarday I "Cardiopatie e gravidanza" *Cuore e Circol* 1948 XXXII 12.

#### Anesthesia and Surgical Operations

- Adams H D and Hand L V "Twenty Minute Cardiac Arrest with Complete Recovery" *J.A.M.A* 1942 CXVIII 133
- Bailey C. C and Betts R H "Cardiac Arrhythmias Following Pneumonecctomy" *New England J Med* 1943 CCXXIX, 356
- Beck, C. S "Resuscitation from Cardiac Standstill and Ventricular Fibrillation Occurring During Operation." *Am J Surg* 1941 LIII 273
- Currens J H White P D and Churchill E H "Cardiac Arrhythmias Following Thoracic Surgery" *New England J Med* 1943 CCXXIX, 360
- Hyman A S "Resuscitation of Stopped Heart by Intracardial Therapy Further Use of Artificial Pacemaker" *U.S Naval M Bull* 1935 XXXIII 205
- Kurtz, C M Bennett, J H and Shapiro H. H "Electrocardiographic Studies During Surgical Anesthesia" *J.A.M.A* 1936 CVI 434
- Levy A. G "The Genesis of Ventricular Extrasystoles under Chloroform with Special Reference to Consecutive Ventricular Fibrillation" *Heart* 1913-14 V 299
- Mallory M., et al "Circulatory Disturbances in Prostatic Hypertrophy" *Ann Int Med* 1943 XVIII 835

#### Recent References (1944-1950)

- Beck, C. S Pritchard, W H and Feil H. S "Ventricular Fibrillation of Long Duration Abolished by Electric Shock" *J.A.M.A* 1947 CXCV 985

- McQuiston W O "Anesthetic Problems in Cardiac Surgery in Children" *Anesthesiology* 1949 X 590
- Ziegler R F "The Cardiac Mechanism During Anesthesia and Operation in Patients with Congenital Heart Disease and Cyanosis," *Bull Johns Hopkins Hosp* 1948 LXXXIII 237

### Excessive Ingestion of Food and Fluid and Salt

- Bollinger "Über die Häufigkeit und Ursachen der idiopathischen Herzhypertrophie in München" *Deutsch med Wchnschr* 1884 X 180
- Clark J H "Acute Cardiac Dilatation An Ever Present Danger in Intravenous Injections" *JAMA* 1927 LXXIX 21
- Ellis L M "The Relative Importance of Salt and Fluids in the Management of Congestive Heart Failure" *Tr New England Heart A* 1942 p 33
- Proger S et al "The Effects of the Ingestion of Excessive Amounts of Sodium Chloride and Water on Patients with Heart Disease" *Am Heart J* 1942 XXIII 555
- Schemm F R "High Fluid Intake in Management of Edema Especially Cardiac Edema I Details and Basis of Regime" *Ann Int Med* 1942 XVII 952
- II Clinical Observations and Data *Ibid* 1944 XXI 937
- Schroeder H A "Studies on Congestive Heart Failure I Importance of Restriction of Salt as Compared to Water" *Am Heart J* 1941 XXII 141
- Wheeler E O Bridges W C and White P D "Diet Low in Salt (Sodium) in Congestive Heart Failure" *JAMA* 1947 CXXXIII 16
- Widal and Lemierre "Pathogenie de certains oedemes brightiques Action du chlorure de sodium ingere" *Bull et mem Soc med d hop de Paris* 1903 XX 678

### Gastrointestinal Diseases and Disorders

- Breyfogle H S "The Frequency of Coexisting Gall bladder and Coronary Artery Disease" *JAMA* 1940 CXIV 1434
- Garvin C F "Cardiac Curshoss" *Am J M Sc* 1943 CCV 515
- Gilbert N C LeRoy G V and Fenn G K "The Effect of Distention of Abdominal Viscera on the Blood Flow in the Circumflex Branch of the Left Coronary Artery of the Dog" *Am Heart J* 1940 XX 519
- Hodge G B and Messer A L "The Electrocardiogram in Biliary Tract Disease and During Experimental Biliary Distention Clinical Observations on 76 Patients" *Surg Gynec and Obst* 1948 LXXXVI 617
- Jones C M "Hiatus Esophageal Hernia with Special Reference to Comparison of Its Symptoms with Those of Angina Pectoris" *New England J Med* 1941 CCXXV 963
- Levine S A and Tranter C L "Infarction of the Heart Simulating Acute Surgical Abdominal Conditions" *Am J M Sc* 1918 CLV 57
- Louis V "Electrocardiographic Aspects of Epidemic Hepatitis" *Schweiz med Wchnschr* 1945 LXXV 986
- Taquini H C Yodice A and Taquini A C "Efecto de la distension vesicular sobre el corazon sano y con infarto de miocardio aguda y cronico experimental" *Rev argent de cardiol* 1947 XIV 117
- Walsh B J Bland E F Taquini A C and White P D "The Association of Gall Bladder Disease and of Peptic Ulcer with Coronary Disease A Post Mortem Study" *Am Heart J* 1941 XXI 689
- White P D "Differential Diagnosis of Gastro-intestinal and Cardiac Disorders (The Alvarez Lecture)" *Am J Digest Dis* 1937 IV 650

### Renal Diseases and Uremia (see also references under Poisoning)

- Ellis A W M "Heart Failure in Acute Nephritis" *Quart J Med* 1936 V 533
- Langendorf H and Pick, A "Elektrokardiogramm bei akuter Nephritis" *Acta med Scandinav* 1938 XCVI 80
- Master A M Jaffe N L and Dack E "The Heart in Acute Nephritis" *Arch Int Med* 1937 LX, 1016
- Rubin M I and Rapoport M "Cardiac Complications of Acute Hemorrhagic Nephritis" *Am J Dis Child* 1938 LV 244

- Whitehill M ■ Longcope W T and Williams ■ "The Occurrence and Significance of Myocardial Failure in Acute Hemorrhagic Nephritis" *Bull Johns Hopkins Hosp* 1939 LXIV ■
- Wood J E Jr and White P ■ "The Electrocardiogram in Uremia and Severe Chronic Nephritis with Nitrogen Retention" *Am J M Sc* 1925 CLXIX 76

#### Recent References (1944-1950)

- LaDue J S and Ashman R "Electrocardiographic Changes in Acute Glomerulonephritis" *Am Heart J* 1946 XXXI 685
- Langendorf R and Pirani C L "The Heart in Uremia" *Am Heart J* 1947 XXXIII 282
- Sawyer W H "Salt Losing Nephritis Simulating Adrenocortical Insufficiency" *New England J Med* 1949 CCXL 210

#### Collagen Diseases and Allergy

- Baggenstoss A H and Rosenberg E F "Cardiac Lesions Associated with Chronic Infectious Arthritis" *Arch Int Med* 1941 LXVII 241
- Banks ■ M "Is There a Common Denominator in Scleroderma Dermatomyositis Disseminated Lupus Erythematosus the Libman Sacks Syndrome and Polyarteritis Nodosa?" *New England J Med* 1941 CCXXV 433
- Clark E "Serum Carditis the Morphologic Cardiac Alterations in Man Associated with Serum Disease" *J.A.M.A* 1938 CX 1098
- Guion C M and Adams E C "Six Autopsied Cases of Disseminated Lupus Erythematosus" *Am J M Sc* 1943 CCV 33
- Klemperer P Pollack A D and Baehr G "Pathology of Disseminated Lupus Erythematosus" *Arch Path* 1941 XXXII 569
- "Diffuse Collagen Disease Acute Disseminated Lupus Erythematosus and Diffuse Scleroderma" *J.A.M.A* 1942 CXIX 331
- Libman E and Sacks B "A Hitherto Undescribed Form of Valvular and Mural Endocarditis" *Arch Int Med* 1924 XXXIII 701
- Rich A R and Gregory J E "Experimental Demonstration that Periarteritis Nodosa Is Manifestation of Hypersensitivity" *Bull Johns Hopkins Hosp* 1943 LXXII 65
- Weiss S Stead E A Jr Warren J V and Bailey O T "Scleroderma Heart Disease With Consideration of Certain Other Visceral Manifestations of Scleroderma" *Arch Int Med* 1943 LXXI 749
- Wilcox H B Jr and Andrus E C "Anaphylaxis in the Isolated Heart" *J Exper Med* 1938 LXVII 169

#### Recent References (1944-1950)

- Baehr G and Pollack A D "Lupus Erythematosus and Scleroderma" *J A M A* 1947 CXXXIV 1169
- Bradfield J Y and Hejtmancik M R "Cardiac Disease and Rheumatoid Arthritis" *Arch Int Med* 1950 LXXXVI 1
- Bywaters E G L "The Relation between Heart and Joint Disease including Rheumatoid Heart Disease and Chronic Post Rheumatic Arthritis (Type Jaccoud)" *Brit Heart J* 1950 XII 101
- Clark W ■ "Rheumatoid Arthritis Case 155 Medical Grand Rounds Massachusetts General Hospital" *Am Pract & Dig Treat* 1950 I 1203
- Duff ■ L "The Diffuse Collagen Diseases Morphological Correlation" *Canad M A J* 1948 LVIII 317
- Griffith G C and Vural I L "Polyarteritis Nodosa A Correlation of Clinical and Postmortem Findings in Seventeen Cases" *Circulation* 1951 III 481
- "Acute and Subacute Disseminated Lupus Erythematosus A Correlation of Clinical and Postmortem Findings in Eighteen Cases" *Circulation* 1951 III 492
- Hench ■ ■ Kendall E C Stocumb C H and Polley H F "The Effect of a Hormone of the Adrenal Cortex (17 hydroxy 11-dehydrocorticosterone Compound E) and of Pituitary Adrenocorticotrophic Hormone on Rheumatoid Arthritis Preliminary Report" *Proc Staff Meet Mayo Clin* 1949 XXIV 181
- Humphreys E M "Cardiac Lesions of Acute Disseminated Lupus Erythematosus" *Ann Int Med* 1948 XXVIII 12

- Mathisen A K and Palmer J D Diffuse Scleroderma with Involvement of the Heart *Am Heart J* 1947 XXXIII 366
- Montgomery H and McCreight W G Disseminate Lupus Erythematosus *Arch Dermat & Syph* 1949 LX 356
- Rich A R Hypersensitivity to Iodine as a Cause of Periarthritis Nodosa *Bull Johns Hopkins Hosp* 1945 LXXVII 43
- Robles Gil J Heart Lesions in Some Rheumatic Diseases Not Including Rheumatic Fever Study of 360 Cases of Rheumatoid Arthritis and 6 of Diffuse Scleroderma *Am Heart J* 1949 XXXVII 667
- Rosenberg E F Bishop L F Jr Weintraub II J and Hensch P S Cardiac Lesions in Rheumatoid Arthritis A Summary of Recent Developments and a Bedside Study of Patients and Controls *Arch Int Med* 1950 LXXXV 751
- Zeller M Temporal Arteritis Case Report *Ann Allergy* 1948 VI, 148

## Miscellaneous Conditions

- Binford C H Primary Amyloid Disease of Myocardium and Blood Vessels Report of Case with Death from Myocardial Failure *Arch Path* 1940 XXIX 314
- Boeck C Multiple Benign Sarcoid of Skin *J Cutan & Genito Urin Dis* 1899 XVII 543
- Donzelot E L insuffisance cardiaque bronzee *Arch des mal du coeur* 1936 XXIX 1
- Longcope W T Sarcoidosis or Besnier Boeck Schaumann Disease *JAMA* 1941 CCVII 13-1
- Muller C Angina Pectoris in Hereditary Xanthomatosis *Arch Int Med* 1939 XLIV 675
- Sheldon J H *Haemochromatosis* Oxford University Press London 1945
- Taquini A C Cooke W T and Schwab II S Observations on the Cardiovascular System in Myasthenia Gravis *Am Heart J* 1940 XX 611
- von Bonsdorff B Less Common Causes of Heart Disease *Acta med scand* 1939 C 320

## Recent References (1944-1950)

- Ballinger J Amyloid Heart Disease *Am J M Sc* 1949 CCXVII 308
- Dahlin D C Primary Amyloidosis with Report of Six Cases *Am J Path* 1949 XXV 105
- Secondary Amyloidosis *Ann Int Med* 1949 XXXI 105
- Davies J N II Endo Myocardial Necrosis Dissertation presented at the University of Bristol June 1948
- Fisch C "The Heart in Dystrophia Myotonica" *Am Heart J* 1951 XLI 525
- Freiman D G Medical Progress Sarcoidosis *New England J Med* 1948 CCXXXIX 664
- Graef I Newman W and Olivett R G Cardiac Manifestations of Hemochromatosis Abstract Program 22nd Scientific Sessions American Heart Association June 1949 p 26
- Griffin W R Nelson H G and Seal J R Hemochromatosis with Auricular Fibrillation A Case Report *Am Heart J* 1950 XXXIX, 904
- Hejtmancik M R Bradfield J Y Jr and Miller G V Myocarditis and Friedreich's Ataxia A Report of Two Cases" *Am Heart J* 1949 XXXVIII 757
- Johnson J B and Jason R S Sarcoidosis of the Heart *Am Heart J* 1944 XXVII 246
- Kulka W E Sarcoidosis of the Heart A Cause of Sudden and Unexpected Death *Circulation* 1950 I 772
- Lindsay M "The Heart in Primary Systemic Amyloidosis" *Am Heart J* 1946 XXVII 419
- Lorenz T H Kurtz C M and Shapiro H II "Cardiopathy in Friedreich's Ataxia (Spinal Form of Hereditary Sclerosis) Review of Literature and Analysis of Cases of Five Siblings" *Arch Int Med* 1950 LXXXVI 412
- McCort J J Wood R H Hamilton J B and Ehrlich D E "Sarcoidosis A Clinical and Roentgenologic Study of Twenty-eight Proved Cases" *Arch Int Med* 1947 LXXX 293

- Nadas A ■ Alimurung M M and Sieracki L S "Cardiac Manifestations of Friedreich's Ataxia" *New England J Med* 1951 CCXLIV 231
- Nothacker W G and Netsky M ■ "Myocardial Lesions in Progressive Muscular Dystrophy" *Arch Path* 1950 L 578
- Perelson H N and Cosby R S "The Electrocardiogram in Familial Periodic Paralysis" *Am Heart J* 1949 XXXVII 1126
- Petit D W Hemochromatosis with Complete Heart Block *Am Heart J* 1945 XXIX 253
- Schick B and Sperry W M "Essential Xanthomatosis: Fifteen Years Observation in Case Occurring in Family with Hypercholesteremia" *Am J Dis Child* 1949 LXXVII 164
- Schulze Buschoff H Spang K and Stollreiter H "Herz und Kreislauf bei der Hemochromatose" *Deutsch Arch f klin Med* 1948 CXIII 416
- Selye H "The General Adaptation Syndrome and the Diseases of Adaptation" *J Clin Endocrinol* 1946 VI 117
- Woolf C R "Primary Systemic Amyloidosis with Gross Cardiac Involvement" *South African M J* 1950 XXIV 146
- Yesner R and Silver M "Fatal Myocardial Sarcoidosis" *Am Heart J* 1951 XLI 777
- Zatuchni J et al "The Heart in Progressive Muscular Dystrophy" *Circulation* 1951 III 846

---

PART III

STRUCTURAL CARDIOVASCULAR  
ABNORMALITIES

---



---

## CHAPTER 24

---

### IMPORTANCE, DIAGNOSIS, AND INCIDENCE OF STRUCTURAL CARDIOVASCULAR ABNORMALITIES

---

In order to keep this volume within reasonable bounds in size which the addition of accounts of important new advances has already threatened to exceed it has proved possible to condense considerably certain portions of Part III in particular the chapters on Myocardial Disease and on Vascular Disease. The reader is referred for further details to the sections on Pathology in the chapters of Part II of this book and to publications on pathology and on the peripheral circulation per se.

The consideration of structural alterations in the heart and great vessels naturally follows a discussion of the fundamental causes that are responsible for them. Although this pathologic field is important it is often neglected. A generation and more ago it was the chief subject for discussion in heart disease and was much too predominant but then a vigorous reaction took place and the pendulum swung too far the other way interest became overwhelmingly centered on physiologic aspects of the circulation with a disregard of actual cardiovascular lesions. A return to a study of structural pathology has been a healthy sign.

Structural abnormalities of the heart affect often to a very important degree the mechanics and the functional state of the circulation. Not only may high blood pressure, infection, endocrine deficiency, anemia, and blood chemical influences seriously affect the heart with little to be found structurally wrong with it unless the conditions are chronic but pathologic lesions alone in their turn too may cause serious cardiovascular strain as in the case of mitral stenosis, aortic regurgitation, myocardial infarcts, and congenital defects. We may find the cause of heart failure and death in one of these organic lesions just as we may find it in some condition entirely outside of the heart and great vessels. It behooves us therefore to look for structural abnormalities in every cardiac patient as well as for evidence as to etiologic factors and as to the functional state of the circulation. Such search is now routinely carried out by



the usual methods of examination which include inspection palpation auscultation roentgenology and electrocardiography, and now cardiac catheterization is also becoming routinely available to aid especially in the diagnosis of certain abnormalities congenital and acquired by x-ray visualization of the catheter and by determination of the blood oxygen content and pressure in the superior vena cava right atrium right ventricle and pulmonary artery (see Chapters 10 and 13 in particular)

Much has appeared in the medical literature about mistakes in diagnosis including the diagnosis of heart disease, and there have been various efforts to correlate antemortem and postmortem diagnoses. It has been shown that more careful history taking and physical examination including more correct appraisal of auscultatory findings as well as the use of other methods of study like electrocardiography and roentgenology have in recent years reduced greatly the errors of cardiovascular diagnosis, but there are likely to remain some pathologic conditions that cannot be diagnosed clinically. In other words not only may errors arise from carelessness or incomplete study but errors may also be due to the very fact that some structural abnormalities give rise to no clinical symptoms or signs and so even under the most favorable circumstances are undiagnosable. Such abnormalities include (1) acute or lesser grades of chronic endocarditis involving valves or heart chambers with little or no valvular deformity (2) lesser grades or earlier stages of coronary atherosclerosis and narrowing (3) slight aortic disease whether aortitis or atheromatosis (4) relatively slight myocardial involvement consisting of hypertrophy of muscle fibers or of degenerative or inflammatory changes and (5) acute or chronic pericarditis of lesser degrees without friction rub or definite signs of effusion enlargement compression or fixation of the heart. Moreover sometimes the very first attack of coronary insufficiency or the onset of acute coronary thrombosis may be rapidly fatal.

Errors of diagnosis may thus be divided into three groups: first those that are preventable because they are due to well marked lesions and should be discovered if careful and complete examinations are made; second those that may or may not be preventable because the lesions are slight to moderate in degree and sometimes give signs and sometimes do not; and third those that are so slight or cause so little strain that no signs ever result. Most of the diagnostic errors in cardiovascular disease when careful clinical work is done fall into this last category and the clinician need feel no chagrin when the pathologist discovers some slight lesion that could be of no clinical importance or could give rise to no symptoms or signs.

Since the clinical diagnosis of organic heart and aortic disease is based on the finding of enlargement valvular lesions pericarditis aortic dilatation and congenital defects (except in a few cases without these findings but with angina pectoris or important abnormalities in cardiac function revealed by electrocardiography) it may be said that about 2 per cent of the population of much of the world show during life signs of organic heart disease through the presence of structural cardiovascular abnormalities varying very much with age from less than 1 per cent in childhood to 10 per cent or even much

more in old age increasing with each added decade. Many of such abnormalities are of little importance, often of far less importance than symptoms like angina pectoris in cases that happen to show no signs of structural defects. At postmortem examination the pathologist finds that far more than 15 to 2 per cent of hearts or great vessels show abnormalities. Most of these abnormalities are however small and unimportant and do not constitute real disease or else they are terminal and not diagnosable clinically. Nearly half of all cases examined post mortem at the Massachusetts General Hospital from 1896 to 1919 showed cardiovascular lesions (1906 out of 4000 autopsies) but these were often trifling (Cabot 1926).

Of patients actually seeking advice because of cardiac symptoms or signs the percentage of those with organic lesions, that is structural abnormalities, varies considerably in different groups, for example from 22 per cent in a small group of cases noted in private practice (Cabot 1926) to 62 per cent in a larger group (1000 cases) seen in consultation (White and Jones 1928) and 87 per cent in a group of 1000 general hospital cases (White and Jones 1928). Since many individuals with symptoms or signs of cardiac nature never visit the hospitals but nevertheless are sufficiently bothered to consult their own private doctors, the last figure is much too high to represent the average. Cabot's series is too small to have any but suggestive value, although it is quite likely that it is near the correct figure for the community at large, including all individuals with cardiac symptoms or signs who do not bother to obtain medical advice. Of the total of those cases who because of cardiac symptoms or signs do visit doctor or hospital the intermediate figure of 50 per cent probably represents reasonably well the number who have organic heart disease.

Of the various abnormalities enlargement of the heart is by far the most common, with valvular disease next and aortic disease, pericarditis and congenital defects less frequent. Of a series of 1846 cases with cardiovascular lesions found at postmortem examination at the Massachusetts General Hospital Cabot reported that 1209 (65.5 per cent) were recognized by the pathologist as having some enlargement of the heart (Cabot 1926); in many of those who showed no enlargement in this series the lesions were too trivial to be dignified by the term disease. Myocardial infarcts were recorded in only 26 cases (1.3 per cent), acute in 20. Valvular defects (but not necessarily deformity sufficient to cause either regurgitation or stenosis) were present in 21 per cent of 1230 autopsied cases of Cabot's cardiac series, including latent as well as manifest lesions. Pericarditis was present as an acute, often terminal condition in 9.1 per cent of 1906 cases of his series, and as a chronic, often silent condition in 6 per cent more, while syphilitic aortitis was found in 5 per cent, aneurysms in 2 per cent, and congenital defects in 1.5 per cent. In comparison among the last 100 cases with significant cardiovascular lesions autopsied at the Massachusetts General Hospital (September 1949) there were 70 cases with cardiac enlargement, 47 cases of myocardial infarction (16 acute, 31 chronic), 26 cases of valvular defects (7 mitral alone, 4 aortic alone, 15 both), 0 tricuspid, 5 cases of acute pericarditis, 7

cases of chronic pericarditis, 3 cases of syphilitic aortitis 0 cases of aortic aneurysms (dissecting in 0) and 3 cases of congenital defects

Of a series of 1 000 clinical cases of organic heart disease in northeastern United States Dublin reported (1925) that 88 per cent showed cardiac enlargement, 44 per cent mitral stenosis 15 per cent aortic insufficiency, 3 per cent aortic stenosis 17 per cent aortitis and 1+ per cent aneurysms Of another clinical series of 2,314 cases of organic heart disease in New England 47 per cent showed valvular disease, 4 per cent syphilitic aortitis 3 per cent pericarditis 2 per cent congenital defects 0.5 per cent aneurysms and the large majority showed definite cardiac enlargement (White and Jones 1928) this series included many private patients living in an enlightened community and had much less syphilis than the other groups cited a state of affairs still more evident now with the passage of time—at present far fewer than 1 per cent of my own private patients have syphilis even as a latent condition

The pathologic lesions found in cases of sudden death are also of especial interest In one series of 198 individuals (Bedford 1933) organic heart disease was found in 122 (62 per cent) of whom 81 per cent were males and 19 per cent females Nonvalvular disease (87 cases) was over twice as common as valvular disease (35 cases) Atherosclerosis of the coronary arteries of an important degree was present in 63 cases (57 males and 6 females) in 33 patients there was gross myocardial fibrosis with definite infarction in 27 and in 6 rupture of the heart wall had occurred at the apex of the left ventricle Gross fatty infiltration of the heart was found in 2 females The aortic valve alone was diseased in 20 cases the mitral valve alone in 7 and both in 8 An aneurysm of the aorta was found in 22 cases of the dissecting variety in 2 Syphilitic aortitis involving the coronary artery mouths occurred in 13 cases

In another series of 130 cases of sudden death (Munck 1931) 74 (57 per cent) showed well marked coronary artery disease and 33 (25 per cent) had syphilitic aortitis

In two of the largest series of autopsied cases of sudden death there were the following findings (1) 2 000 in number (Martland 1940), organic heart or aortic disease was found in 1 590 (79.5 per cent) 1 115 of which were of coronary or hypertensive type 262 syphilitic 116 rheumatic while 731 showed extensive coronary artery disease of which 304 had acute thrombosis and (2) 2 030 in number (Helpern and Rabson 1945), cardiovascular disease in 49 per cent of which more than half were coronary cases (see Chapter 34 for further details)

Of some special interest is a recent analysis of the postmortem findings at the Massachusetts General Hospital and Boston City Hospital (Medalia and White 1951) of individuals dying at the age of 50 years or more This gives some idea of the expected findings in older people The following were the incidences of the 'underlying and contributing causes of death' in both males and females (Table 11)

A report has just been published from the Geriatric Clinic of the Peter Bent Brigham Hospital in Boston entitled *Diseases in Old Age A Clinical and Pathological Study of 7 941 Individuals Over 61 Years of Age* (Monroe

Table 11

THE PREVALENCE OF UNDERLYING AND CONTRIBUTING CAUSES  
OF DEATH AFTER THE AGE OF 50 IN 1 251 INDIVIDUALS  
AT THE MASSACHUSETTS GENERAL AND BOSTON  
CITY HOSPITALS

	6th Decade	7th Decade	8th Decade	9th Decade
Totals	313	340	286	312
Coronary sclerosis	144	224	222	262
Atherosclerosis including coronary sclerosis	215	243	251	305
Nephrosclerosis	71	107	111	171
Cerebrovascular lesions	32	31	43	60
Bronchopneumonia	81	116	105	147
Liver and gallbladder disease	44	84	68	81
Cancer	68	83	85	67
Tuberculosis	39	30	34	14
Gastric and duodenal ulcers	25	20	26	21

1951) Clinically only 44.6 per cent of the patients in this series had no heart disease but the pathologists found a much smaller fraction than that for only 28.5 per cent of the men and 28.3 per cent of the women had normal hearts out of 1 177 autopsies. The heart weights at autopsy were compared. In the normal men 61 to 85 years old the heart weights ranged from 302 to 373 gm while in the normal women of the same age the weights ranged from 274 to 304 gm. In the cases of valvular heart disease the average weight of the heart in old men was 549 gm and in old women 439 gm. Finally the heart weight in cases of nonvalvular disease averaged 526 gm in old men and 426 gm in old women when there was coronary artery occlusion and 493 gm in the old men and 394 gm in the women without coronary artery occlusion.

In all this discussion of structural changes in the heart and great vessels it is of the utmost importance to recognize the wide range of the normal, a range which has not yet been adequately determined and the very wideness of which makes it difficult or impossible to identify slight abnormalities. For a full discussion of the range of the normal heart the reader is referred to Chapter 2 and for certain normal measurements to Table 12 which appears at the end of this chapter. One particular measurement as an example may be appropriately referred to here, namely that of heart weight.

The normal heart weight bears a fairly definite relation to body weight, 0.40 to 0.45 per cent, but ranging from 0.35 to 0.50 per cent, lower values being found more often in women and obese individuals and higher values in men and thin persons. The normal heart weight may be calculated from the body weight with an error up to about 10 per cent. The weight of the heart in the normal adult male averages about 300 gm and in the female about 250 gm. The limits of the normal range of weight of the adult heart are 200 and 350 gm. Heart weight has been related also to body length (Zeek, 1942). Heart volume and certain other measurements are to be found in Table 12.

Table 12

## NORMAL ANATOMIC CARDIAC MEASUREMENTS

WEIGHT (gm)		VOLUME AND CAPACITY (cc)		OTHER MEASUREMENTS (adult)	
<b>Adult</b>		<b>Heart tissue (Beneke)</b>		<b>Ventricular wall thickness</b>	
Range	200-350	Birth to 3 months	70-25	(midway between base and apex and not including papillary muscles)	
Average male	300	1 year	30-35		
Average female	250	6 years	65-75		
Percentage of body weight (Smith)		10 years	110	Left	10-12 mm
male	0.43%	15 years	130-175	Right	3-4 mm
female	0.40%	Adult	210-290	Ventricular septum	9-12 mm
<b>Child (Vierordt Muller)</b>		<b>Capacity of chambers in adult (average) (Hochrein)</b>		<b>Valve circumferences (cm)</b>	
Birth	20-25			Tricuspid	11-15
1 month	15-20			(Average 1)	
6 months	20-25	Right atrium	163	Mitral	9-11
1 year	30-40	Right ventricle	137	(Average 10)	
2 years	45-55	Left atrium	140	Pulmonary	8-9
4 years	65-75	Left ventricle	171	Aortic	7-8
8 years	95-105	Total (4 chambers)	561		
12-16 years	150-250			<b>Valve areas (sq mm) (Creutzfeldt)</b>	
<b>Left ventricle right ventricle</b>		Thus the total volume of the filled heart averages 811 cc (561 + 250) from these figures during life the heart volume is never so great since all four chambers are not full at the same time—thus would mean a subtraction of about 200 cc from the volume stated above leaving approximately 600 cc		Tricuspid	~160
Birth 1 l				Mitral	160
Adult				(Dexter et al)—During life	4 000-6 000
Range 17 l to 195 l				Mitral	
Average 185 l					
<b>Individual chambers (adult)</b>				<b>Heart length (longitudinal diameter in cm)</b>	
Left ventricle	130			(Average 11 cm)	10-1
Right ventricle	70				
Left atrium	24			<b>Heart width (transverse diameter in cm)</b>	8-10
Right atrium	25			(Average 9 cm)	
				<b>Heart depth (anteroposterior diameter in cm)</b>	6-8
				(Average 7 cm)	

## BIBLIOGRAPHY

## INTRODUCTION TO STRUCTURAL CARDIOVASCULAR ABNORMALITIES

## SEE ALSO REFERENCES IN THE FOLLOWING CHAPTERS OF PART III

- Baillie M *The Morbid Anatomy of Some of the Most Important Parts of the Human Body* J Johnson and J Nicol London 1793 Chapters I and II
- Hedford T H B "Pathology of Sudden Death Review of One Hundred and Ninety eight Cases Brought in Dead" *J Path & Bact* 1933 XXXVI 333
- Beneke F W *Ueber das Volumen des Herzens und die Weite der Arteria pulmonalis und Aorta ascendens in den verschiedenen Lebensaltern* Theodor Kay Cassel 1879
- Bonetus T *Sepulchretum* Leonard Chouet Geneva 1679 2nd ed (Mangetus) 1700
- Cabot R C *Facts on the Heart* W B Saunders Co Philadelphia 1926
- Creutzfeldt *Das Flächenwachstum der menschlichen Atrioventrikularklappen* G Neuhahn Jena 1897
- Dublin L I "Statistical Aspects of the Problem of Organic Heart Disease" *New York State J Med* 1925 XXV 983 and *Am Heart J* 1926 I 359

- Karsner H T Rothschild, L and Crump E S "Clinical Diagnosis as Compared with Necropsy Findings in Six Hundred Cases" *J.A.M.A.* 1919 LXXIII 666
- Kaufmann R "Über autopsische Befunde bei Herzkrankheiten" *Med Klin* 1927 XXIII 1919
- Keith A "The Functional Anatomy of the Heart" *Brit M J* 1918 I 361
- Levine V and Carr J G "Cardiac Weights" *Arch Int Med* 1933 LII 429
- MacCallum J B "On the Muscular Architecture and Growth of the Ventricles of the Heart" *Johns Hopkins Hosp Rep* 1900 IX 307
- Mahaim I and Benatt A "Nouvelles recherches sur les connexions supérieures de la branche gauche du faisceau de His-Tawara avec la cloison interventriculaire" *Cardiologia* 1937 I 61
- Mall F P "On the Muscular Architecture of the Ventricles of the Human Heart" *Am J Anat* 1911 XI 211
- Martland H "Sudden Deaths with Reference to Their Prevention" *Proc New England Heart A* 1940 p 42
- Monckeberg, J G Ribbert H Jores L Benda C and Winkler L "Herz und Gefäße Vol II of *Handbuch der speziellen pathologischen Anatomie und Histologie* Julius Springer Berlin 1924
- Morgagni G B *De Sedibus et Causis Morborum* Ex typog Remondiniana Venice 1761
- Müller W *Die Massenverhältnisse des menschlichen Herzens* Leopold Voss Hamburg and Leipzig 1883
- Munck W "Sudden Death from Heart Failure in Adults" *Ugeskr f Læger Copenhagen*, 1931 XCIII 787
- Nonidez J F "Studies on the Innervation of the Heart I Distribution of the Cardiac Nerves with Special Reference to the Identification of the Sympathetic and Parasympathetic Ganglia" *Am J Anat* 1939 LXV 361
- "II Afferent Nerve Endings in the Large Veins and Arteries" *Ibid* 1941 LXVIII 151
- Robb J ■ "The Structure of the Mammalian Ventricle and the Mammalian Auricle" *Am Woman's J* 1934 XLI 65
- Robb J S and Robb R C "The Normal Heart" *Am Heart J* 1942 XXIII 455
- Rosahn P D "Weight of Normal Heart in Adult Males" *Yale J Biol & Med* 1941 XIV 209
- Smith H L "The Relation of the Weight of the Heart to the Weight of the Body and of the Weight of the Heart to Age" *Am Heart J* 1928 IV 79
- Vierordt H *Anatomische physiologische und physikalische Daten und Tabellen zum Gebrauche für Mediziner* Gustav Fischer Jena 3rd ed 1906 (1st ed 1881)
- White P D and Jones T D "Heart Disease and Disorders in New England" *Am Heart J* 1928 III 302
- White P D Sprague H ■ and Jones T D "The Correlation of Clinical and Pathological Findings in Cardiovascular Disease" *J Iowa State M Soc* 1926 XVI 479
- Zeek P M "Heart Weight I Weight of Normal Human Heart." *Arch Path* 1942 XXXIV 8-9

#### Recent References (1944-1950)

- Helpern M and Rabson S M "Sudden and Unexpected Natural Death—General Considerations and Statistics" *New York State J Med* 1945 XLV 1197
- Kisch ■ et ■ "Electron Histology of Heart. I" *Exp r Med & Surg* 1948 VI 329
- Lendrum, A C., et al "Pulmonary Changes Due to Cardiac Disease with Special Reference to Haemosiderosis" *Quart J Med* 1950 IX 249
- Lev M and Simkins S "Architecture of the Human Ventricular Myocardium" *Am Heart J* 1949 XXXVII 647
- Medalia L S and White P ■ "Diseases of the Aged An Analytical Study of Pathological Findings in 1251 Autopsy Protocols in the Aged" 1951 in press
- Monroe R T *Disease in Old Age* Harvard University Press Cambridge 1951
- Pannier R "Contribution à l'innervation sympathique du cœur Les nerfs cardioacelerateurs" *Arch Internat de Pharmacol et Ther* 1946 LXXIII 193

---

## CHAPTER 25

---

### MYOCARDIAL DISEASE CARDIAC ENLARGEMENT HYPERTROPHY AND DILATATION MYOCARDITIS

---

The myocardium is the most important part of the heart. If it is sound a great deal of disease of endocardium and pericardium and great vessels of valvular deformities and septal defects and of strain from hypertension can be endured for a surprising number of years if it is seriously diseased or fails death may come quickly even though all the rest of the cardiovascular system is perfect.

Myocardial disease includes various abnormalities. The most common are hypertrophy and dilatation (due fundamentally to the strain of greatly increased work) and the degeneration and fibrosis due to coronary insufficiency. Less frequent are inflammatory changes or true myocarditis, atrophy, toxic and malnutritional changes, fatty degeneration from severe anemia, fatty infiltration, congenital defects, neoplasms, and traumatic lesions.

Dilatation of the heart chambers is a very common condition occurring sometimes as a compensatory reaction to valvular disease and sometimes as a natural sequence of a failing heart muscle under the effect of the conditions which cause myocardial disease itself.

Enlargement of the heart, which includes both hypertrophy of muscle and dilatation of chambers, will be considered first since it is by far the most common of all cardiac abnormalities.

#### CARDIAC ENLARGEMENT HYPERTROPHY AND DILATATION

Cardiac enlargement is the commonest and most important evidence of heart disease. Often it can be taken as an index of the degree of cardiac strain, since a very large heart indicates a great cardiovascular burden and an unfavorable prognosis while a small heart indicates a small degree of cardiac strain and a favorable prognosis except in the presence of serious coronary

disease It is to be noted at the outset that very important heart or aortic disease may be present with little or no enlargement examples of this are occasional cases of syphilitic aortitis of angina pectoris and of coronary narrowing leading shortly to thrombosis with cardiac infarction Usually however a diseased heart is enlarged and its increase in size can be made out in many cases by clinical study alone although roentgenologic control is often invaluable

Enlargement of the heart may be due to hypertrophy dilatation or both The combination in varying degrees is much commoner than either condition alone except for very slight hypertrophy discoverable only at autopsy It is the dilatation rather than the hypertrophy that accounts for most of the increase in volume especially of the largest hearts In fact hypertrophy alone or with little dilatation may increase the heart size extraordinarily little and in early stages is not discoverable clinically as in the case of many patients with hypertension A preponderant muscle weight increase gives rise to the so-called concentric hypertrophy of the heart When in the course of time the heart begins to fail and grossly to dilate or when there is a constant demand for an increased output as in aortic regurgitation the hypertrophy is associated with dilatation and is then called eccentric Another factor influencing the so-called concentric and eccentric types of hypertrophy is the state of the heart muscle at the time of death and at the postmortem examination if the heart stops in systole (contracted) the appearance of concentric hypertrophy is increased if in diastole (dilated) the appearance of eccentric hypertrophy is increased

Enlargement of the heart up to a weight of 425 gm may exist in a big man without clinical signs but hypertrophy of the heart beyond that weight should be found by clinical study Dilatation occurs as an important secondary factor if dilatation is absent slight cardiac hypertrophy may exist with no clinical evidence thereof except on occasion when studies are carried out serially by x ray or precordial electrocardiography, if dilatation is present the heart may be obviously enlarged clinically with little or no hypertrophy as in some cases of acute dilatation following acute coronary thrombosis with myocardial infarction

The cause of cardiac enlargement is heart strain whether intrinsic that is due to valvular disease myocardial infarction or true myocarditis (as in acute rheumatic fever) or extrinsic due to hypertension chronic thyrotoxicosis or severe anemia The strain may be acute or chronic overwhelming or slight The speed of enlargement of the heart and the preponderance of hypertrophy or of dilatation appear to depend in part on these factors of time and degree A quick occlusion of a large coronary artery may result in rapid cardiac enlargement due to dilatation with the development of hypertrophy on recovery On the other hand hyperpiesia (essential hypertension) slowly beginning causes only gradual enlargement hardly to be made out on clinical examination and consisting primarily of hypertrophy the dilatation appearing later when the heart begins to fail and to enlarge more rapidly Mitral stenosis simi



larly acts slowly on the heart size involving the right ventricle instead of the left

The most common factors of heart strain giving rise to enlargement of the heart are hypertension of the essential type valvular disease of rheumatic or syphilitic origin and myocardial infarction Even in New England where rheumatic heart disease is the commonest of all clinical types producing cardiac symptoms and signs cardiac enlargement is more often found at postmortem examination without than with valvular disease

Less common causes of cardiac enlargement than hypertension and valvular disease are true myocarditis (especially during a severe rheumatic infection in childhood) cardiac infarction from severe coronary disease thyrotoxicosis chronic pulmonary disease (extensive fibrosis as in silicosis) and congenital defects Rare causes are arteriovenous aneurysms severe anemia beriberi hypothyroidism (myxedema) thoracic and spinal deformities chronic pericarditis with external adhesions and cardiac neoplasms Finally cardiac enlargement is occasionally of unknown cause undoubtedly there exist causes of enlargement still unrecognized or poorly understood A few possible factors not yet clearly recognized as causes of cardiac enlargement are as follows a severe infection rheumatic or otherwise may cause so much myocardial damage that the heart dilates and does not recover sufficiently to return to its normal size whether the valves are damaged or not excessively severe or prolonged physical strain as in athletic sports may rarely in the case of a sensitive heart produce some permanent cardiac enlargement prolonged and excessive tachycardia in certain arrhythmias (especially atrial flutter and fibrillation) may be to blame in a minority of patients so afflicted but particularly in infants a rare case of congenital idiopathic cardiac hypertrophy of lesser degree may survive to adolescence or adult life a combination of two or more of these factors is the most probable of all Therefore it is unwise as yet to label every large heart of unknown type hypertensive without more proof

*Hypertrophy* Hypertrophy consists of the increase in size of the individual muscle fibers and apparently not in their increase in number at least in adults although MacMahon (1937) has reported finding in infants and children a true active proliferation of the heart (with mitotic nuclear division) and regeneration of the myocardium following severe injury A comparative study has been reported of the size of muscle fibers seen in a normal heart weighing 300 gm in a hypertrophied heart weighing 500 gm and in an atrophied heart weighing 165 gm The ratio of muscle fiber size was 5 9 4 respectively (Karsner, Saphir and Todd 1925) An important feature of myocardial hypertrophy after maturity is the apparent failure of the blood supply to parallel in its growth that of the muscle fibers the ratio of one capillary to one muscle fiber in the adult remains throughout life no matter how large the heart becomes resulting in a relative coronary insufficiency in an enlarged heart compared to the normal (Roberts and Wearn 1941)

Whether the increased work and strain alone are primarily responsible or whether the hypertrophy is the reaction to trauma of the muscle fibers and primary dilatation due to the strain as has been suggested we do not know but we are aware of the fact that increase of the bulk and weight of the myocardium commonly follows considerably increased work if long sustained and that it occurs in the part of the heart primarily involved. Although the heart is made up of complex masses of muscle continuous between the ventricles and between the atria respectively hypertrophy and enlargement may be very limited in location as in the case of left ventricular hypertrophy in hyperpiesia and of right ventricular hypertrophy in pulmonary valve stenosis. When other factors like congestive failure appear the enlargement spreads to involve other parts of the heart for example, a failing hypertensive heart with functional mitral regurgitation shows secondary enlargement of left atrium and of right ventricle. Although it is common in the end stages of heart disease and failure or in combined strains to find general enlargement of the whole heart it is important to recognize that at first the enlargement may be entirely limited to one heart chamber sometimes with slight atrophy of another and that such limited enlargement may persist for years or that it may always preponderate. A discussion of the factors responsible for enlargement of the individual heart chambers will begin on page 650. All of the muscle of the heart wall of any given chamber whether atrial or ventricular (and including the papillary muscles) apparently takes part in the hypertrophy. Finally it is important to realize that a structurally sound hypertrophied heart muscle may dilate and fail even though the muscle cells show no degeneration post mortem.

In 1910 Bernheim introduced the concept of right ventricular obstruction and failure secondary to marked bulging of the septum into its cavity in cases of gross hypertrophy of the left ventricle. However the adaptability of the eccentric right ventricle to such a heart shape and the rarity of convincing proof have caused a debate as to the existence of such an entity (Evans and White 1948 Russek and Zohman 1950 Wilson and Zimmerman 1950).

**Dilatation** Dilatation of the heart is a very common condition frequently occurring along with hypertrophy as a part of cardiac enlargement. It consists of a stretching of the heart wall due to a weakening or atonic state of the muscle or to a response to the physiologic demand for an increased output of blood per beat (as in exercise or in compensation for valvular regurgitation or anemia). If the cause of such acute dilatation ceases the heart regains its usual size unless the injury has been irreparable. Often the dilatation persists or increases with continuance of the strain the tone of the muscle may partly recover but a permanent stretching of the fibers may persist. In some instances enlargement of the heart due preponderantly to dilatation may decrease clearly under observation as in occasional cases of acute or subacute rheumatic carditis during convalescence occasional cases of congestive failure from any

cause under treatment with rest and digitalis cases of anemia under specific therapy, some cases of hypertensive heart disease treated by thoracolumbar sympathectomy and cases of the myxedema heart under thyroid therapy

*Hypertrophy and dilatation* The largest hearts are usually the heaviest hearts since hypertrophy and dilatation are almost invariably associated and when a heart is so large that it reaches almost to the chest wall on the left and considerably over halfway to that on the right it will be found in the adult to weigh from 500 to 1 000 gm

A few instances occur in which a single chamber is much dilated this is almost always the left atrium which in cases of mitral valve deformity with atrial fibrillation may become enormous large enough to hold a liter and a half of fluid or more and to fill a large part of the thoracic cavity extending across the mediastinal space to the right as well as to the left The left atrium may be much larger than all the rest of the heart, which is attached to the atrium like an appendage the term 'aneurysm of the atrium' has been applied to such cases Both atria may be greatly increased in volume as shown in Figures 120 121 and 122 The enlargement is almost wholly due to a stretching of the atrial wall but the muscle is somewhat thickened also The largest left atrium on record is said to have had a capacity of 3 liters (Minkowski 1904) I have encountered one holding 1 760 cc (Figures 121 and 122), there are records of two other left atria larger than this 2½ liters (Muller 1905) and 2 liters (Goedel 1929)

The heaviest heart—*cor bovinum* found with marked aortic regurgitation or stenosis or extreme hypertension of long standing—may weigh as much as 1 000 gm over three times the normal The heaviest heart recorded is said to have weighed 58½ oz (1 755 gm) and showed aortic and mitral valvular disease and a moderate degree of adhesive pericarditis of rheumatic origin in a man 28 years old (Smith 1850) the heart referred to above with the enormous left atrium pictured in Figures 121 and 122 weighed 850 gm and showed well marked but not extreme mitral stenosis and regurgitation and very slight aortic stenosis

Preponderant enlargement of either ventricle tends to give a rather characteristic shape to the heart like an egg with blunt end at the base of the heart in the case of a large left ventricle and more spherical in the case of a large right ventricle The more hypertrophy and the less dilatation there are in left ventricular enlargement the more the heart shape resembles that of preponderant right ventricular enlargement, the more the dilatation of the left ventricle the longer is the heart

The factors responsible for enlargement of the left ventricle are as follows for hypertrophy with little or no gross dilatation uncomplicated chronic hypertension is mostly responsible and aortic stenosis occasionally (Figure 123 page 654) for dilatation with little or no hypertrophy there are serious acute myocarditis as in some cases of rheumatic fever and diphtheria acute myocardial infarction of large size acute high grade anemia and severe trauma for hypertrophy and dilatation we may blame aortic regurgitation mitral regurgitation

chronic high grade anemia rarely chronic adhesive pericarditis and most often left ventricular failure complicating chronic hypertension aortic stenosis, and myocardial infarction from acute coronary occlusion



FIG 120 Roentgenogram of thorax showing enormous heart shadow in a case of chronic rheumatic heart disease with mitral and tricuspid stenosis. Male PW age 35. Note that the right heart border touches the right border of the thorax.

The factors responsible for enlargement of the right ventricle are as follows: for hypertrophy with little or no gross dilatation the most common cause is failure of the left ventricle without failure of the right; an occasional cause is mitral stenosis and rare causes are extensive pulmonary fibrosis, pulmonary endarteritis and congenital pulmonary stenosis (Figure 124 page 655); for dilatation with little or no hypertrophy we may find serious acute myocarditis as in some cases of rheumatic fever and diphtheria, acute high grade anemia, severe trauma and acute massive obstruction in the pulmonary circulation from pulmonary embolism (acute cor pulmonale); for hypertrophy and dilatation right ventricular failure complicating left ventricular failure is most

FIG 121 Photograph showing marked enlargement of the heart due to dilatation of left atrium, right atrium and right ventricle in a young man with mitral stenosis and regurgitation and atrial fibrillation. The volume of the filled heart was 4 600 cc its weight empty was 850 gm and the chambers had the following capacity: left atrium 1 760 cc, right atrium 650 cc, right ventricle 330 cc and left ventricle 70 cc. Anterior view. A heart model of normal size is shown for comparison. The arrow points to the interventricular sulcus. LA = left atrium, LV = left ventricle, RA = right atrium, RV = right ventricle. (A full description of this exceptionally large heart was published in the *JAMA* 1931 XCVI 840.)

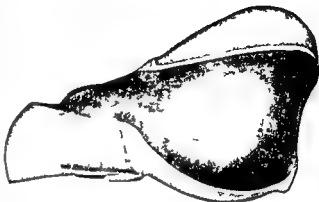
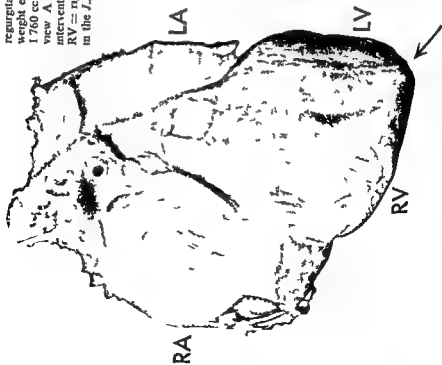




FIG 122 Right lateral (A) and left lateral (B) views of heart shown in Figure 121. Note backward bulging of the left atrium best seen in the left lateral view. LA = left atrium, RA = right atrium, LV = left ventricle, RV = right ventricle.

commonly the cause with mitral stenosis pulmonary stenosis and the chronic cor pulmonale as occasional factors and less often tricuspid valve disease chronic high grade anemia chronic severe thyrotoxicosis, congenital idiopathic hypertrophy and pulmonary regurgitation



FIG 123 Photograph showing a heart with a much hypertrophied left ventricle (in a case of aortic stenosis) The left ventricular wall measured 2 cm in thickness (normally 1.0 to 1.2 cm)

It is evident that several factors act simultaneously on both ventricles to cause acute dilatation and chronic dilatation and hypertrophy but uncomplicated hypertrophy of either ventricle is independent of the other when hypertrophy of the right ventricle follows hypertrophy of the left ventricle there is always an essential element of dilatation of the left ventricle as a part of the sequence

*Enlargement of the left atrium* is chiefly the result of dilatation and occurs more markedly with mitral valve disease but also often with failure of the left ventricle Similarly *enlargement of the right atrium* is chiefly due to dilatation and results from tricuspid valve disease or much more commonly from failure of the right ventricle

Finally interesting but rare types of general cardiac enlargement are those found in infancy and once called congenital idiopathic hypertrophy Cases of glycogen storage (von Gierke's) disease (von Gierke 1929 Pompe 1933) of myocarditis of unknown cause of coronary anomalies and of excessively

rapid rates in paroxysmal tachycardia (Hubbard 1941) have lately been separated out leaving only a minority now unexplained. The heart weights in these various conditions are often several times the normal (Figure 74 page 324) and the prognosis is bad except in the cases of tachycardia which recover when properly treated.



FIG 174 Photograph showing marked right ventricular hypertrophy in chronic cor pulmonale. M.C. male age 49. Three years after beginning of exposure to silica dust in gritty-soap factory. Death due to complicating pneumonia. RA = right atrium RV = right ventricle (kindness of Oxford University Press chapter by P. H. White on Cor Pulmonale).

#### MYOCARDIAL DEGENERATION AND FIBROSIS CARDIAC RUPTURE CARDIAC ANEURYSM CALCIFICATION

*Myocardial degeneration and fibrosis* result chiefly from extensive coronary atherosclerosis with obstruction to the blood supply of the myocardium. If the deficiency is gradual in its progress so is the myocardial change which begins as scattered or local fatty degeneration and necrosis and ends in replacement of a certain number of muscle fibers by connective tissue (fibrosis) or in some slight degree of regeneration of muscle if the blood supply is soon enough re-established by collateral circulation. If the deficiency is abrupt and extensive in the amount of muscle involved an infarct results which may heal as a firm scar (see Figures 106A 106B and 107 pages 532 533 and 535) or may proceed to aneurysm or rupture of the heart wall.

Myocardial necrosis and fibrosis can also result from other causes than coronary atherosclerosis though less commonly Syphilitic or embolic (chiefly



by bacterial vegetations) occlusion of the coronary mouths and high degrees of aortic stenosis also may rarely produce such lesions, three cases of myocardial infarction due to syphilitic stenosis of the coronary ostia among 6 225 consecutive autopsies in New Orleans have been recently reported (Burch and Winsor 1942) Disseminated areas of ischemic necrosis may result from carbon monoxide poisoning or very severe anemia (Friedberg and Horn 1939), and Davies (1948) has described endomyocardial necrosis and fibrosis in Africans

Cardiac aneurysm and rupture long recognized pathologically have only in recent years been properly attributed in the great majority of cases to coronary thrombosis with myocardial infarction Both cardiac aneurysm and rupture are as a rule only postmortem findings unrecognized for the most part before autopsy although they have been diagnosed in an increasing number of cases of late especially cardiac aneurysm by the aid of roentgenology (Figure 125)

*Rupture of the heart* usually occurs a few days after acute myocardial infarction sets in due to friability of the heart wall Among 25 000 autopsies at the Los Angeles County Hospital from 1924 to 1941 there were 865 cases of unhealed myocardial infarction 72 of these (or 8 per cent) showed cardiac rupture 13 involving the septum (Edmondson and Hoxie 1942) the threat of such an accident is a very potent reason for insistence on absolute rest during the first fortnight after acute coronary occlusion In a series of 27 mentally ill patients with acute myocardial infarction 20 of which were clinically undiagnosed and hence untreated rupture of the heart caused death in 16 (73 per cent) (Jetter and White 1944) in contrast to the average findings of 5 to 10 per cent in the wards of a general hospital as further exemplified by a series of 10 cases of cardiac rupture (9.5 per cent) among 105 patients with acute myocardial infarction (Friedman and White 1944) Rupture rarely if ever occurs in cases of chronic or healed myocardial infarction it was found in none of 165 such cases in Friedman and White's series. It takes place within the first two weeks of the infarction most commonly at the end of the first week. Cardiac rupture usually ends in instantaneous death but in some cases when the tear in the wall is small and the intrapericardial leak of blood gradual death may be postponed for hours finally resulting from hemopericardial tamponade (see Chapter 27) unless relieved by paracentesis not a likely procedure in such cases Cardiac rupture may rarely result from gumma pyogenic abscess tuberculous lesion echinococcus cyst malignancy and trauma Rupture of papillary muscles and interventricular septum may also occur spontaneously in fresh myocardial infarction

*Cardiac aneurysm* in slight degree is very common in fact it is present in nearly every case of extensive myocardial infarction When aneurysms of the heart were first described several centuries ago they referred to general enlargement of the heart or of its chambers but in recent years the term has been reserved for local pouches or sacs in the heart wall The cardiac aneurysm begins as an acute lesion and if no rupture occurs it becomes chronic with little or no danger of rupture after the first fortnight it varies in size from a

slight bulge of the wall to an enormous cavity as large as the rest of the heart. Sometimes it contains a thrombus which may send off emboli. The aneurysm is located as a rule either on the anterior and left wall of the left ventricle near the apex frequently involving a bit of the lower part of the interventricular septum (Figure 106A page 532) or on the posterior wall of the left ventricle high up. These two sites are the usual locations of cardiac infarcts due most commonly to occlusion of the descending branch of the left coronary artery in the one case and to occlusion of the right coronary artery or the circumflex branch of the left in the other case. Other but rare locations of cardiac aneurysms are the upper part of the interventricular septum where the aneurysm may be also of congenital origin and the outer wall of the right ventricle. Most



FIG 125 Roentgenogram of thorax showing cardiac aneurysm consequent to myocardial infarction H. O. D., male age 39 (kindness of Dr A. N. Ferguson Fort Wayne Ind.)

cardiac aneurysms are small or shallow and undiagnosable in life the largest ones are easily diagnosed by roentgen ray, appearing as a bulge at the left border of the heart above the apex in the usual anteroposterior view and showing often an alarming but apparently benign degree of expansile pulsation during systole (Figure 125 page 657)

Marked dilatation of either atrium especially of the left has been called aneurysmal but this is a general and not a localized enlargement Aneurysmal pockets in valve cusps and sinuses of Valsalva have also been described due usually to bacterial endocarditis and rarely to congenital defects There is no special treatment for cardiac or valvular aneurysms except that strain on the heart should be carefully limited

*The deposition of lime salts in the heart muscle (calcification)* is occasionally found chiefly where there has already been myocardial disease particularly degeneration following infarction from coronary closure There is a disturbed local metabolism in such cases as there is at the base of the heart valves at times and in chronic valvular lesions with calcification of the cusps in whole or in part The lime salts are most often found in the papillary muscles of the left ventricle or in the septum or anterior wall near the apex of the left ventricle Irregular areas of calcification occur varying in size from that of a pea to that of a walnut They may cast a shadow by roentgen ray which distinguishes them from the heart muscle about them A cardiac aneurysm may be outlined roentgenologically by calcification of its wall In very rare cases actual bone is found instead of mere masses of lime salts

## MYOCARDITIS

Myocarditis or true inflammation of the myocardium occurs in rheumatic fever and in severe cases of diphtheria infrequently in cardiovascular syphilis and rarely in other infections like virus and rickettsial diseases (except in scrub typhus tsutsugamushi fever when it is more common), typhoid fever tuberculosis trichiniasis trypanosomiasis, hydatid disease and pyemia (see Chapters 14, 16 and 17) it can be diagnosed clinically only by the realization of the frequency of mild to moderate involvement of the myocardium in these infections and in a few cases circumstantially by the finding of acute heart block abnormal electrocardiograms or acute cardiac dilatation without definite valvular lesions coronary disease or hypertension to account for the dilatation In an analysis of 1 402 cases of myocarditis diagnosed post mortem Gore and Saphir (1947) have presented a number of interesting ratios of the incidence of this condition in various diseases Some of these ratios where more or less adequate numbers of cases were involved are as follows myocarditis was found in 144 of 221 cases of diphtheria 5 of 135 cases of malaria 9 of 581 cases of tuberculosis 2 of 66 cases of syphilis 5 of 41 cases of schistosomiasis 1 of 400 cases of epidemic hepatitis 32 of 222 cases of virus pneumonia 13 of 144 cases of acute encephalitis 13 of 94 cases of poliomyelitis, 11 of 48 cases of coccidioidomycosis 1 of 16 cases of tularemia, 14

of 160 cases of acute glomerulonephritis, 7 of 44 cases of exfoliative dermatitis and 3 of 12 cases of Boeck's sarcoid. The discussion of the various etiologic types of myocarditis has been included in detail in appropriate chapters in Part II of this book.

There are in addition three kinds of myocarditis of unknown cause: one occurring in earliest infancy in fact probably in fetal life to give rise to one type of congenital cardiac hypertrophy (Kugel and Stoloff 1933); a second called Fiedler's isolated myocarditis and acute interstitial myocarditis of rare and obscure nature with tendency to sudden death to be further discussed below; and a third also obscure and rare occurring in variable degree in adults with cardiac enlargement which leads to congestive failure or sudden death (Levy and von Glahn 1937). Whether or not these three groups are related as varying results of the same underlying condition is not known.

The clinical diagnosis of myocarditis so freely used in the past has wrongly included many other conditions in particular the frequent instances of hypertensive heart disease in which there is cardiac hypertrophy and enlargement but no inflammatory reaction in the muscle; the term myocarditis has also wrongly included frequent instances of coronary heart disease in which degenerative changes, fibrosis and atrophy may occur without actual inflammatory process. In the attempt to diagnose heart disease more accurately the term myocarditis is wisely being abandoned in large part; we must remember nevertheless that there does exist such a condition as myocarditis which is in particular exemplified by involvement by rheumatic fever and diphtheria.

### FIEDLER'S MYOCARDITIS

In 1899 there was published in the *Festschrift zur Feier des fünfzigjährigen Bestehens des Stadtkrankenhauses zu Dresden-Friedrichstadt* a paper of sixteen pages entitled "Ueber akute interstielle Myokarditis" (Concerning Acute Interstitial Myocarditis) by Dr. A. Fiedler, chief physician to the City Hospital at Dresden. Quotations from this interesting paper are as follows (translation by myself):

Based on the clinical records and autopsy findings of four cases who died and on the record of an additional patient who survived the disease there has been presented herewith the description of an acute inflammation of the myocardium generally coming on very abruptly and with a chill which is almost certainly of microparasitic origin.

This disease attacks as a rule young people and runs its course with little or no fever. The pulse rate is almost always very much accelerated and very rarely reduced. The heart is dilated both to right and to left. The heart action is irregular and dyspnea, cyanosis, evidences of stasis in both greater and lesser circulations and a great tendency to heart weakness are constantly present.

I cannot convince myself that we are dealing in these cases with an ordinary septic infection. To my mind it is much more evident that a microorganism, differ

ent from the usual agents producing sepsis is responsible localized directly in the heart muscle and setting up there an inflammatory reaction or that a poison is produced which reaches the heart by the blood stream and affects particularly the interfibrillary tissue of the myocardium

In diphtheria, scarlet fever and exanthematic typhus that in diseases which are caused by entirely different infectious agents and which differ also so widely in their clinical manifestations we find, as mentioned above interstitial myocardial changes very similar to those in the cases which I have observed and described herein

We may conclude that in all these different diseases one and the same poison does not produce these myocardial changes but that entirely different infectious agents are present which cause this inflammation either directly or indirectly

I would not fail to mention that even though interstitial myocarditis is always preponderant this designation is not to be accepted in the strictest and exclusive sense of the word The interstitial changes in the muscular tissue were the first and most important but as microscopic investigation showed there was also always present a parenchymatous inflammation too consisting of slight changes in the muscle fibres themselves

And now still a few words about the prognosis of the disease in question as mentioned above our cases ended as a rule fatally This does not however force the conclusion that all of these cases have a bad prognosis

Microscopic sections of the myocardium in those cases who survived only a few days after the onset of chill and serious illness showed invasion of the myocardium with small round cells and beginning disintegration of the myocardial fibers

Therefore the designation of this disease as purely interstitial (or isolated) is misleading One might better term it acute myocarditis of unknown cause although there is no reason why one may not add 'Fiedler's type' in parenthesis after such a description It is quite possible that an acute fulminant virus myocarditis may be the answer If the etiologic factor is evident it should be so stated and the designation 'Fiedler's' omitted In time all such cases may be separated off from the one time useful eponym

## ATROPHY OF THE HEART MICROCARDIA

Atrophy may be dismissed with two observations (1) When relative disuse or inanition or Addison's disease is responsible for the atrophy the heart actually decreases somewhat in bulk and weight in whole or in part with slight decrease in size of the muscle fibers such atrophy is infrequent and slight in most cases Atrophy is sometimes seen in the left ventricle in well marked mitral stenosis and in the whole heart in a few cases of chronic constrictive pericarditis and in bedridden patients as in chronic tuberculosis Marked atrophy of the left ventricle has been produced in the experimental animal by an artificial tricuspid valve lesion (Stadler 1907) (2) If degeneration or inflammation causes local atrophy partial fibrosis results but the heart as a

whole does not decrease in size or weight if it must still keep up an active circulation in fact there may develop a compensatory hypertrophy

True microcardia if it exists must be very rare it has been reported as a congenital anomaly at birth but further confirmation is necessary

### TOXIC AND MALNUTRITIONAL MYOCARDIAL CHANGES

In rare cases there are myocardial changes of noninfectious toxic origin and others associated with malnutrition and avitaminosis (see Chapter 23) Chloroform carbon monoxide benzol and the toxins of eclampsia and uremia have been noted as factors responsible for focal necroses and severe malnutrition with vitamin deficiency as in beriberi and rachitis has occasionally caused myocardial degeneration and edema with dilatation of the heart Upon specific therapy both the general malnutritional edema and the cardiac dilatation tend to subside it is thought that in especially severe cases in children congestive heart failure may supervene to cause death (Waring Charleston S C personal communication 1936) In scorbutus hemorrhages may occur throughout the heart As a matter of fact avitaminosis tends to be multiple and therefore to show multiple effects both generally and in the heart

Sensitivity to the sulfonamides has also been reported as a cause of damage to the myocardium which may be reversible (Lilienfeld et al 1950 Mayer and Levy 1950)

### FATTY DEGENERATION IN SEVERE ANEMIA

Associated with the cardiac dilatation and hypertrophy that result from severe anemia there is a characteristic fatty degeneration of certain parts of the heart muscle farthest removed from the arterial ends of the capillaries giving rise to a curious striped appearance which has occasioned the term tiger or tiger lily heart Otherwise fatty degeneration is but a part of the effect of severe infections like diphtheria or of infarction due to serious coronary disease

### FATTY INFILTRATION

Fatty infiltration of the myocardium especially involving the right ventricle is a definite entity most common in middle aged and elderly women In extreme cases the wall of the right ventricle is found largely composed of layers of fat infiltrated between the muscle bands In rare cases this condition has been blamed as the primary or secondary cause of heart failure When excessive it may be merely a part of generalized fatty infiltration in other organs and throughout the body

### AMYLOID DISEASE XANTHOMA HEMOCHROMATOSIS SARCOIDOSIS

Rare affections of the myocardium of obscure origin include amyloid disease xanthoma hemochromatosis and sarcoidosis which tend to be but part

of a general process of amyloid xanthomatous and iron deposition and sarcoid infiltration throughout the body (see Chapter 23) When such processes have become evident elsewhere, as for example in the skin and the heart is enlarged or in other respects abnormal showing for instance otherwise unexplained heart block by electrocardiogram it is reasonable to suspect that these diseases have involved the heart

## BIBLIOGRAPHY

### ABNORMALITIES OF MYOCARDIUM AND OF HEART CHAMBERS

SEE ALSO REFERENCES IN CHAPTERS 7 CARDIOVASCULAR ROENTGENOLOGY 9 ELECTROCARDIOGRAPHY 13 CONGENITAL CARDIOVASCULAR DEFECTS 14 RHEUMATIC HEART DISEASE 15 BACTERIAL ENDOCARDITIS 16 CARDIOVASCULAR SYPHILIS 17 OTHER INFECTIONS 21 CORONARY HEART DISEASE AND CORONARY OCCLUSION AND 23 OTHER ETIOLOGIC FACTORS AND RELATIONSHIPS

#### Cardiac Enlargement

- Bernheim De l'asytôle veineuse dans l'hypertrophie du coeur gauche par sténose concomitante du ventricule droit *Rev de Med* 1910 XXX 785
- Bland E F Balboni G M and White P H Enormous Increase of Heart Volume with Mitral Stenosis Report of a Case *JAMA* 1931 XCVI 840
- Davis D and Blumgart H L "Cardiac Hypertrophy Its Relation to Coronary Arteriosclerosis and Congestive Heart Failure" *Ann Int Med* 1937 XI 10 4
- Edens E "Über Herzhypertrophie" *Deutsch Arch f klin Med* 1913 III 288
- Eyster J A E Cardiac Dilatation and Hypertrophy *Tr A Am Physicians* 19 XLII 15
- Goedel A Eine ungewöhnliche Form der Herzvergrößerung (enorme Vorhofvergrößerung) bei Mitralstenose *Wien klin Wchnschr* 1929 XLII 4-7
- Herrmann G R and Wilson F N "Ventricular Hypertrophy A Comparison of Electrocardiographic and Postmortem Observations" *Heart* 1922 IX 91
- Hochrein M "Untersuchungen am venösen Teil des Kreislaufes I Herzkapazität" *Arch f exper Path u Pharmacol* 1927 CXXIV 341
- Hubbard J P Paroxysmal Tachycardia and Its Treatment in Young Infants" *Am J Dis Child* 1941 LXI 687
- Karner H T Saphir O and Todd T W "The State of the Cardiac Muscle in Hypertrophy and Atrophy" *Am J Path* 1925 I 351
- Kugel M A Enlargement of the Heart in Infants and Young Children" *Am Heart J* 1919 XVII 602
- Levy R L and Rousselot L M Cardiac Hypertrophy of Unknown Etiology in Young Adults A Clinical and Pathological Study of Three Cases" *Am Heart J* 1931 IX 178
- Lewis T Observations upon Ventricular Hypertrophy with Especial Reference to Preponderance of One or Other Chamber" *Heart* 1914 V 367
- MacMahon H E Hyperplasia and Regeneration of Myocardium in Infants and in Children" *Am J Path* 1937 XIII 845
- Minkowski "Demonstration eines Herzens mit ungewöhnlich starker Dilatation der Vorhöfe" *Munch med Wchnschr* 1904 LI 182
- Müller G "Ungewöhnliche Dilatation des Herzens und Ausfall der Vorhofsfunktion" *Ztschr f klin Med* 1905 LVI 520
- Newton F C and Levine S A "Decompression of Chest for Dysphagia Due to Marked Cardiac Enlargement" *J Thoracic Surg* 1942 XII 151
- Pompe J C "Hypertrophie idiopathique du coeur" *Ann d'anat path et d'anat norm med chir* 1933 X 23

- Roberts, J T and Wearn J T "Quantitative Changes in the Capillary Muscle Relationship in Human Hearts During Normal Growth and Hypertrophy" *Am Heart J* 1941 XXI 617
- Rosenow E C Jr and Smith H L "Extreme Cardiac Hypertrophy Report of Forty four Cases in Which the Heart Weighed 800 Grams or More" *Minnesota Med* 1939 XXII 739
- Smith H L of Randolph Vi Reported to the Society by Prof A Clark Case of Monstrous Hypertrophy of the Heart" *New York J Med* 1850 V 207
- Stadler E Experimentelle und histologische Beiträge zur Herzhypertrophie. *Deutsch Arch f klin Med* 1907 XCI 98
- Stroud W D "The Importance and the Most Satisfactory Clinical Methods of Estimating the Myocardial Reserve" *Am Heart J* 1926 I 334
- Thompson W P and White P D "The Commonest Cause of Hypertrophy of the Right Ventricle—Left Ventricular Strain and Failure" *Am Heart J.* 1936 XII 641
- von Gierke F Hepato nephromegalia glycogenica" *Beitr z path Anat u z allg Path* 1929 LXXIII 497

#### Recent References (1944-1950)

- Dafey R and Franks R "Massive Dilatation of the Left Auricle" *Quart J Med* 1949 XVIII 81
- Evans L R and White P D "Massive Hypertrophy of the Heart with Special Reference to Bernheim's Syndrome" *Am J Med Sc* 1948 CCXVI 485
- Russek H I and Zohman B L "The Syndrome of Bernheim as a Clinical Entity" *Circulation* 1950 I 759
- Wilson E B Jr and Zimmerman S L Bernheim's Syndrome Considered in the Light of a Fatal Case" *Am J Med Sc* 1950 CCXX 247
- Atrophy Myocardial Degeneration and Fibrosis Cardiac Aneurysm and Rupture Calcification Myocarditis Other Myocardial Disease**
- Benson R L Hunter W C and Manlove C H "Spontaneous Rupture of the Heart Report of 40 Cases in Portland Oregon" *Am J Path* 1933 IX 295
- Brown C E and Evans W D "Primary Massive Calcification of the Myocardium" *Am Heart J* 1940 XIX 106
- Burch G E and Winsor T "Syphilitic Coronary Stenosis with Myocardial Infarction" *Am Heart J* 1947 XXIV 740
- Burn C G Holland A G and Crawford J H "Rare Cardiac Aneurysm in a Child" *Am Heart J* 1943 XXVI 415
- Clawson B J "Myocarditis" *Am Heart J* 1948 IV 1
- Danzonlot E "L'insuffisance cardiaque bronzée" *Arch d mal du coeur* 1936 XXIX 1
- Edmondson H A and Horie H J "Hypertension and Cardiac Rupture" *Am Heart J* 1947 XXIV 719
- Fiedler A "Ueber akute interstitielle Myokarditis" *Festschrift d Stadtkrankenhauses Dresden Friedrichstadt* 1809
- Flaxman N "Myocardial Abscess" *JAMA* 1943 CXXII 804
- Friedberg C K and Horn H "Acute Myocardial Infarction Not Due to Coronary Artery Occlusion" *JAMA* 1939 CXII 1675
- Hoffmeyer J "Xanthomatosis in Vascular System" *Nord med* 1941 IX 365
- Kugli M A and Stoloff E G "Dilatation and Hypertrophy of the Heart in Infants and in Young Children with Myocardial Degeneration and Fibrosis (So-Called Congenital Idiopathic Hypertrophy)" *Am J Dis Child* 1933 XLV 878
- Levy R L and von Glahn W C "Further Observations on Cardiac Hypertrophy of Unknown Etiology in Adults" *Tr A Am Physicians* 1937 LII 259
- Longcope W T and Fisher A M "Involvement of the Heart in Sarcoidosis or Besnier Boeck Schaumann's Disease" *J Mt Sinai Hosp* 1947 VIII 784
- Saphir O "Myocarditis General Review with Analysis of 240 Cases" *Arch Path* 1941 XXXII 1000
- Sheldon J H *Haemochromatosis* Oxford University Press London 1935
- Sternberg, M "Das chronische partielle Herzaneurysma" *Anatomie Klinik Diagnose* Franz Deuticke Leipzig and Vienna 1914



- Tedeschi C G and Stevenson T D Jr Interstitial Myocarditis in Children *New England J Med* 1951 CCXLIV 352
- von Bonsdorff H "Myocardial Disease of Obscure Origin" *Acta med Scandinav* 1939 C 352
- Wood F C and Lavezey M M Five Year Survival After Perforation of Interventricular Septum Caused by Coronary Occlusion *Am Heart J* 1944 XXIV 807

#### Recent References (1944-1950)

- Bedford D E and Konstamm G L S Heart Failure of Unknown Aetiology in Africans *Brit Heart J* 1946 VIII 236
- Brean H P Marks J H Sosman M C and Schlesinger M J "Massive Calcification in Infarcted Myocardium" *Radiology* 1950 LIV 33
- Carloti, J "Étude clinique et anatomique de 14 cas de myocardies" *Arch d mal du coeur* 1948 XLI 498
- Dahlin D C Primary Amyloidosis with Report of Six Cases *Am J Path* 1949 XXV 105
- Davies J N P Endo Myocardial Necrosis Dissertation presented at the University of Bristol June 1948
- Edelstein J M Primary Massive Calcification with Ossification of the Myocardium *Am Heart J* 1946 XXXI 496
- Friedman M and White P D Rupture of the Heart in Myocardial Infarction Experience in a Large General Hospital *Ann Int Med* 1944 XXI 778
- Gore I and Saphir O Myocarditis *Am Heart J* 1947 XXXIV 827
- Jetter W W and White P D "Rupture of the Heart in Patients in Mental Institutions" *Ann Int Med* 1944 XXI 783
- Lilienfeld A Hochstein E and Weiss W Acute Myocarditis with Bundle Branch Block Due to Sulfonamide Sensitivity" *Circulation* 1950 I 1060
- Lindsay S "The Heart in Primary Systemic Amyloidosis" *Am Heart J* 1946 XXXII 419
- McKeown F "Non Rheumatic Interstitial Myocarditis" *Brit Heart J* 1949 XI 417
- Mahaim I "Myocardite aigue Dissolution auriculo ventriculaire masquee (isorythmique et tachysphygmique) Lésions inflammatoires extensives et nécrosantes du faisceau de His Tawara" *Acta Cardiol* 1948 III 121
- Mayer G and Levy A Manifestations cardiaques au cours des accidents dus aux sulfamides *Arch d mal d coeur* 1950 XLIII 525
- Miller G Becker I M and Taylor H K "Auricular Calcification" *Am Heart J* 1950 XL 293
- O Farrell P T "Calcification of Left Auricle" *Irish J M Sc* 1951 May 211
- Santiago Stevenson D and Hellerstein H K "Atrophy of the Heart Clinical Pathological Electrocardiographic Correlation in 85 Proven Cases" *Am Heart J* 1949 XXXVII 672
- Schwartz H and Canelli F R Spontaneous Rupture of Papillary Muscle of the Left Ventricle A Clinical Syndrome *Am Heart J* 1950 XL 344
- Smith J C Rupture of a Papillary Muscle of the Heart Report of Two Cases" *Circulation* 1950 I 766
- Wachstein M "Glycogen Storage (von Gierke's) Disease Predominantly Involving the Heart Report of Case with Histochemical Phosphatase Studies" *Am J M Sc* 1947 CCXIV 401
- Zeek P M Heart Weight II Effect of Tuberculosis on Heart Weight" *Arch Path* 1946 XLI 526

## ENDOCARDIAL AND VALVULAR DISEASE INTRACARDIAC THROMBOSIS

Endocardial disease is chiefly a matter of endocarditis but it includes also infarction (incident to coronary thrombosis) atheroma neoplasm and trauma of the endocardium

### ENDOCARDITIS

Endocarditis or inflammation of the endocardium is made up of several types varying according to the etiologic factors. These etiologic types have been described in detail in Chapters 14, 15, 16, and 17 of this book and will be but briefly summarized here. They are the "rheumatic," subacute bacterial, acute bacterial, terminal verrucose, syphilitic, tuberculous, and other infectious types.

The *rheumatic endocardial involvement* is a simple verrucose lesion with rows of small vegetations or thrombi consisting mostly of fibrin on the valves often located only along the line of closure of the mitral cusps but sometimes situated on other heart valves also where they close (Figure 83, page 362) on the chordae tendineae and on the atrial mural endocardium. Recovery may be complete without deformity and with but little thickening of the valve leaflets but more often there is extensive scarring with contraction and adhesion of the cusps and of the chordae tendineae causing stenosis and regurgitation especially after repeated rheumatic infections. This type of acute endocarditis is rare before the age of 5 years and relatively uncommon after 15.

The *subacute bacterial endocardial involvement* consists primarily of a lesion of the valves with larger vegetations than in the case of rheumatic endocarditis and with more extensive infection of the mural endocardium of atria and of ventricles due to extension of the process from the valves or to contact with infected cusps (Figure 88, page 393). The vegetations contain masses of bacteria usually streptococci of the *viridans* type or products of their degeneration. Chronic healed scarring and deformity are now the rule in subacute bacterial endocarditis because of the lowered mortality from this disease by the use of penicillin in the active stage. Rupture of valve cusps and chordae

tendineae occasionally occurs, and embolism from the endocardial vegetations is very common. This type of endocarditis is commonest between the ages of 18 and 35 years but may occur at any age thereafter or less commonly earlier.

The *acute bacterial endocarditis* is much like the subacute bacterial type except that it is a more fulminating process and now becoming rare. It is caused by any one of a variety of organisms, most commonly by streptococcus pneumococcus, staphylococcus or gonococcus.

*Terminal verrucose endocarditis* resembles the rheumatic type. It is quite common as a complication of many fatal illnesses. It is probable that a non-rheumatic verrucose endocarditis can occur in many patients who recover leaving slightly thickened cusps difficult to distinguish from very mild chronic rheumatic endocarditis but of that we have not yet clear proof.

*Syphilitic involvement of the endocardium* is due to an extension of syphilitic aortitis to the aortic valve causing an adhesion of the cusp ends against the aortic wall which results primarily in a widening of the commissures and secondarily thereby in aortic regurgitation. It should be noted however that the wall of the very first portion of the ascending aorta may be so weakened by the syphilitic process that it dilates and that therefore this dilatation rather than aortic valvular disease may be responsible for some of the widening of the aortic valve commissures and of the resultant aortic regurgitation. Further extension of the syphilitic process from the aortic valve may slightly involve the anterior cusp of the mitral valve.

*Tuberculous endocarditis* consists of the involvement of the endocardium by military tubercles with or without ulceration. It is rare.

Also rare are other infections like actinomycosis and extension to the endocardium of myocardial abscesses.

Combined lesions are frequently found and it is sometimes possible to determine in the pathologic specimens the effect of each individual factor.

## OTHER ABNORMALITIES OF THE ENDOCARDIUM

Other abnormalities of the endocardium include a variety of conditions. Frequently there are unimportant *atheromatous* lesions of the valvular or nonvalvular (mural) endocardium which are similar to areas with early fatty changes in the aorta and coronary arteries but the endocardial lesions progress only rarely to calcified plaques. In some cases with extensive subendocardial calcification the endocardium may be eroded by direct pressure. Occasionally the destructive process associated with myocardial infarction from coronary thrombosis or embolism penetrates to the endocardium to cause ulceration and intracardiac thrombosis over the site of the ulceration. *Mural thrombosis* may however and probably most commonly does develop as the result of stasis rather than of endocardial injury especially in a fibrillating atrium or in a ventricular (as in an aortic) aneurysm. *Neoplasm* and *trauma* of the endocardium are rare (see Chapter 23) as are also *congenital valvular defects* (see Chapter 13). *Diffuse parietal endocardial sclerosis* occurs in rare cases most

commonly in congenital heart disease its pathogenesis is still obscure *Endocardial and subendocardial calcification* is however very frequent and consists of two types the more common being superimposed on old valvular disease mainly rheumatic and the other (Monckeberg's sclerosis) being an independent atherosclerotic process which attacks especially the valve rings and bases but may also invade the cusps It is important to note that chronic endocarditis with extensive valvular deformity may exist even in old age with little or no calcification and that much calcification may occur with little or no evidence of antecedent endocarditis although both processes are to be sure frequently combined the old endocardial scarring doubtless favoring the calcification An interesting very rare dark brown pigmentation (ochronosis) of heart valves aorta cartilage and bone has been ascribed to an inborn fault of tyrosin metabolism (Neumann Brno 1946) Finally *endocardial fibrosis* of unknown origin has been described in Africans by Davies (1948)

### VALVULAR DISEASE OF THE HEART

Valvular disease of the heart is an important subject for consideration not only because it is often the primary cause of heart failure but also because there is much unnecessary confusion associated with it in the medical literature and in the minds of many physicians As noted in Chapter 14 valvular disease is a common structural abnormality wherever the rheumatic infection is frequent it must however be distinguished from valvular incompetence due to cardiac dilatation alone

Valvular disease is caused by acute infection which includes the rheumatic (most commonly) subacute bacterial acute bacterial and terminal verrucose types by syphilitic invasion and rarely by tuberculosis it is sometimes due also to atheromatous and sclerotic changes often with calcification chiefly at the base of the aortic valve without any evidence of infection uncommonly it is due to congenital malformation rarely it is due to trauma either direct or indirect There may be an acute fulminating or terminal involvement or the process may be very chronic consisting of a healed after-effect of some acute process that occurred many years before Often two factors are combined for example subacute bacterial endocarditis superimposed on congenital defects or on chronic rheumatic valvular disease calcification of valves already deformed by infection or rupture of inflamed valves

Valvular disease may be so slight that there is not enough deformity to interfere in any way with the valve function in such cases there may be an entire absence of signs and symptoms On the other hand the valvular defect may be so great that it is itself the cause of much cardiac enlargement and failure Even with objective signs of valvular deformity there may be no disability and life may extend to a ripe old age as in the case of Dr Herman F Vickery who lived to be nearly 84 with a moderate degree of rheumatic mitral stenosis in addition to some coronary insufficiency (White and Bland 1941) A coincidence of coronary heart disease and chronic rheumatic heart

disease is more common than generally recognized (Gardner and White 1949)

It is important always to distinguish between the influence of active disease and that of structural abnormality on the circulation and health. For example acute bacterial endocarditis may show but little valve deformity and yet terminate fatally in a short time because of the toxic effect of the infection or of embolism while chronic mitral stenosis or aortic regurgitation of rheumatic origin though of high degree may allow many years of life with a badly crippled heart. An abnormal valve no matter how slight its deformity is always of some significance because it is a point of less resistance to infection or strain than is a normal valve and sometimes it is but a part of some important acute or chronic disease. These facts are frequently lost sight of in the casual disregard of valvular disease which has been common in the past.

Clinically it is often difficult or even impossible to say whether valvular insufficiency is due to disease of the valve itself or to cardiac dilatation with normal valve or to cardiac dilatation plus valvular disease. Sometimes it is easy to make the differentiation but in certain cases especially in those with advanced heart failure we may utilize without avail all methods of study including percussion auscultation sphygmomanometry roentgenology and graphic methods. In most cases of advanced heart failure it matters little whether the valves are diseased or not so far as prognosis and treatment are concerned. It is in the earlier cases without congestive failure and with relatively little cardiac enlargement that the differentiation between valvular disease and functional defect alone is much more important and is often possible. All methods of examination are sometimes needed in this differentiation one method alone like auscultation or roentgenology may be misleading.

Of the four heart valves the mitral is the one most commonly affected it is damaged in well over half of all cases of valvular disease. Aortic valve disease is next in frequency followed by lesions of the tricuspid valve, which is but rarely deformed to any important extent. The pulmonary valve is very infrequently involved. In a series of 208 cases of valvular disease in New England examined macroscopically post mortem the mitral valve was found diseased in 85.6 per cent the aortic valve in 44.7 per cent the tricuspid valve in 15.9 per cent and the pulmonary valve in 1.9 per cent (Cabot, 1926). The aortic and mitral valves were involved together in 19.2 per cent the aortic mitral and tricuspid in 1.1 per cent the mitral and tricuspid in 2.9 per cent the pulmonary and tricuspid in 1 per cent and all four valves in 1 per cent. In a postmortem series of 126 cases of valvular disease studied in Vienna the percentages of disease of mitral aortic tricuspid and pulmonary valves were 60.76.25 and 0 respectively (Kaufmann 1927) but these patients were all male adults and syphilis accounted for one third of the aortic valve lesions. In a series of 300 autopsied cases of valvular heart disease in Berlin (Sperling 1872) the mitral valve was involved in 85 per cent of all cases and in 52 per cent without other valves affected the aortic valve was involved in 43 per cent altogether and alone in 13 per cent the tricuspid valve in 10 per cent altogether but

alone in only 1 per cent while the pulmonary valve was diseased in only 1 per cent of the total cases and in no case alone. In a series of 1 097 cases in New England in which valvular disease was sufficient or definite enough to be diagnosed clinically 56.3 per cent were thought to have mitral valve disease alone 14.7 per cent aortic alone and 28.9 per cent both aortic and mitral rare cases were thought to have tricuspid valve disease along with mitral disease or with mitral and aortic but in no case of the series was tricuspid valve disease a certainty pulmonary valve disease was diagnosed in no case (White and Jones 1928). In a clinical series of 1 781 cases of valvular disease at the Johns Hopkins Hospital (Hirschfelder 1918) mitral valve disease alone was diagnosed in 51 per cent aortic valve disease alone in 22 per cent and both together in 20 per cent. Why the mitral valve should be most often involved and why the left heart valves are more frequently diseased than those on the right side is not clear. Greater vascularity of the mitral valve has been suggested as a cause but it is probable that the greater force of closure of the mitral and aortic valves allows more readily a lesion produced by direct or indirect bacterial action combined with trauma at their lines of closure than in the case of the right heart valves which are under less pressure except in fetal life when the pulmonary and tricuspid valves are more often involved than the aortic and mitral valves.

The characteristics of the individual valve lesions will now be considered in the order of frequency of valvular involvement mitral aortic tricuspid and pulmonary.

### A. MITRAL VALVE DISEASE

Disease of the mitral valve is common but it is frequently diagnosed when not present because a systolic murmur at the cardiac apex due to cardiac dilatation is wrongly interpreted as due to valvular disease.

**Etiology Cause.** Mitral disease is due in the large majority of cases to rheumatic infection. It may be found either in the acute stage or as a chronic lesion. In the acute stage the rheumatic infection may not be recognized as such either because it gives very obscure or indefinite signs or because no doctor is called at the time or because the doctor who is called is unfamiliar with atypical rheumatism but the resulting heart involvement is generally regarded as rheumatic and is called the rheumatic type probably justifiably. It is possible that other infections especially of focal nature may be sometimes responsible but this still remains to be proved. Subacute and acute bacterial endocarditis are much less frequent causes of mitral disease and until lately were always fatal. Terminal verrucose endocarditis as a complication is not infrequently found in patients who have died from all kinds of diseases it involves the mitral valve most commonly. Atheromatous lesions in the mitral valve are very similar to early atheromatous lesions of the blood vessels they consist of the infiltration and precipitation of lipoids cholesterol crystals and calcium in the leaflets on their ventricular sides suggesting the

importance of mechanical factors (Hellwig 1942) Sclerotic change with calcification at the base of the valve sometimes fixing the annulus as a solid stony ring is infrequently encountered when calcification involves the mitral valve leaflets themselves it is almost invariably superimposed upon antecedent rheumatic mitral stenosis in which case it may further deform the valve sometimes with masses of calcium projecting into heart chambers or even into the atrioventricular ostium to increase the degree of stenosis Tuberculous and syphilitic involvement are very rare as is also congenital deformity in the nature of either stenosis or atresia

**Age** Mitral valve disease is commonly found in youth and middle age, it is less common in old age although both the rheumatic and the sclerotic types are found in old persons in infancy mitral valve disease is very rare

**Sex** The female sex shows a higher percentage of mitral valve disease than does the male in about the ratio of three to two

**Pathology** Although the pathology of endocardial disease whether of inflammatory atherosclerotic or traumatic nature has already been discussed in the earlier part of this chapter and in Chapters 14 15 and 16 the particular pathology of chronic mitral disease needs brief consideration The healing of acute endocarditis may leave no defect in valve function and merely a slight thickening of the valve cusps along their lines of closure With marked or repeated inflammation the damage is greater and the contracting scar tissue may cause all grades of deformity Two processes in particular are responsible for defective function one of these is fusion of the cusps at their commissures causing both stenosis (narrowing of the ostium or opening) and regurgitation (leaking back of the blood stream through the incompetent valve), the other is fusion of the chordae tendineae with shortening which is equally important in deforming the valve In very chronic cases after repeated infections the fusion of the cusps is so pronounced that there is simply a diaphragm or funnel with a narrow ostium in the place where the freely acting mitral cusps should be (Figure 126) The small opening varies in shape and size and it has received a variety of names such as 'buttonhole' and 'fish mouth' Occasionally the damaged valve becomes calcified and absolutely rigid with stony surface exposed to the blood stream through erosion of the endocardium A few instances occur in which a valve cusp is rent or a chorda tendinea torn off its attachment at one end so that the torn fragments float freely at one end or edge in the blood stream The valve ring at its base and sometimes the valve cusps themselves to a greater or lesser extent may become calcified and fixed with more or less stenosis Large vegetations in bacterial endocarditis may sometimes produce a virtual mitral stenosis without actual valve deformity Finally developmental defects and probably infectious lesions may give rise in the fetus to stenosis hypoplasia or even atresia of the mitral valve

Mitral regurgitation and mitral stenosis are almost invariably combined pathologically In rare instances however they may be considered pure (1) when retraction of the relatively undamaged or at least relatively non-adherent valve cusps is caused by shortened contracted and perhaps fused



FIG 176 Photograph showing marked stenosis of the mitral orifice with fish mouth valve and relative tricuspid insufficiency. Note thick wall of left atrium (kindness of Dr Ronald Grant, Guy's Hospital, London.)



chordae tendineae giving rise to mitral regurgitation without stenosis and (2) when the valve cusps are fused giving rise to mitral stenosis without sufficient fibrosis or thickening of the cusp extremities or shortening of the chordae tendineae to allow regurgitation. When the valve opening is rigidly fixed with fibrous or calcified edge in marked mitral stenosis a certain amount of regurgitation necessarily occurs too. Clinically, preponderant mitral stenosis produces a different picture from that of preponderant mitral regurgitation and when the two defects are about balanced the clinical findings show the combined effects of moderate mitral stenosis and moderate mitral regurgitation. From the pathologic point of view it would be more accurate to make a clinical diagnosis of mitral disease with preponderant stenosis or "with preponderant regurgitation" but the shorter terms "mitral stenosis" and "mitral regurgitation" are much simpler for use and sufficiently accurate if we realize that they refer to the clinical results of preponderant defects of the mitral valve.

Functional mitral insufficiency due to left ventricular dilatation should not be regarded as a trivial condition. Often the left ventricular dilatation is the result of serious myocardial disease itself of infarction for example or of left ventricular failure due to the strain of hypertension or of myocardial insufficiency because of serious anemia. It may be due to adhesive pericarditis or it may be a compensatory mechanism with aortic regurgitation. It is possible that the displacement downward of the papillary muscles is the result of the ventricular dilatation is a more important factor in causing the mitral regurgitation than is dilatation of the atrioventricular orifice that is of the valve ring. The chordae tendineae are of limited length and with their attachments to the papillary muscles moved away from the base of the heart their insertions on the valve cusps are likewise displaced downward. This results in an inability of the mitral cusps to close tightly no matter how tautly the chordae may stretch or how normal or elastic the cusps may be. Regurgitation of greater or lesser degree follows. Occasionally in fact frequently factors due both to left ventricular dilatation and to deformities of valve cusps and chordae tendineae combine to cause mitral regurgitation.

Functional mitral stenosis occurs (a) occasionally as a relative stenosis with normal mitral valve but marked left ventricular dilatation (b) in very rare instances of tumor or thrombus in the left atrium large and free enough to obstruct to a variable degree the blood flow through the mitral valve from atrium to ventricle and (c) perhaps to a slight degree in marked aortic regurgitation when the aortic regurgitant blood stream forces back the anterior cusp of the mitral valve.

The average normal circumference of the mitral valve in the adult human heart is 10 cm (ranging from 9 to 11 cm) a circumference less than 7.5 cm may be considered to indicate definite stenosis. The area of the normal adult mitral orifice has a range during life of 4 to 6 sq cm. An area of 1 sq cm or less is found in the case of marked mitral stenosis (Gorlin and Haynes 1950).

*Effects of mitral valve disease on the heart* If the mitral valve lesion results primarily in stenosis the left atrium and right ventricle bear the brunt of the burden the former becoming hypertrophied and dilated and the latter hypertrophied at first and finally dilated also when the strain is much increased. Eventually the right atrium also is involved with dilatation and hypertrophy after the right ventricular dilatation has resulted in more or less constant tricuspid regurgitation. The left ventricle may remain practically unaffected even when the right ventricle and left atrium become double their normal size in fact the left ventricle may be a little smaller than normal. The cardiac apex is sometimes formed in large part by the right ventricle.

If on the other hand regurgitation is the chief defect the left ventricle becomes involved as well as the left atrium and right ventricle. Hypertrophy and dilatation of left ventricle and left atrium and hypertrophy of the right ventricle are the primary effects with dilatation of both right heart chambers later. With marked and chronic mitral regurgitation the heart may become enormous all four chambers being involved. Functional mitral regurgitation will naturally have the same effect on the heart chambers as organic mitral regurgitation of the same degree and chronicity but with functional mitral regurgitation other factors such as heart failure may cause death before enough time has elapsed to duplicate the picture found with organic mitral disease without failure at the onset or recovery from the dilatation and failure (due to anemia or other factors responsible for the functional mitral regurgitation) may permit the valve again to become competent.

Since both defects—stenosis and regurgitation—are generally combined to a greater or lesser degree in cases of organic mitral disease the effects on the heart depend in part on the relative amounts of stenosis and regurgitation and in part on the absolute degree of the valvular disease. With slight mitral regurgitation or stenosis there is scarcely any heart burden and but little change in heart size but when either stenosis or regurgitation is extreme the changes are marked.

High grades of organic mitral stenosis are much more common than are high grades of organic mitral regurgitation and are doubtless better borne. The development of mitral stenosis is a gradual one the earliest defect in rheumatic children being more regurgitant than stenotic. It requires at least two years as a rule for the establishment of mitral stenosis. Mitral murmurs heard during the first year after the onset of a moderate or severe rheumatic infection in a child are to be attributed to dilatation of the left ventricle incident to the rheumatic myocarditis and not to mitral valve deformity (Bland White and Jones 1935) such murmurs may eventually merge into those of mitral valve disease or they may disappear occasionally when recovery is especially satisfactory (Bland Jones and White 1936). The heart and body as a whole gradually develop compensatory mechanisms to take care of the strain of the stenosis often for many years. The rather sudden onset of functional mitral regurgitation with heart failure or its more gradual develop

ment with marked aortic regurgitation may however be a great additional burden for the heart and hasten its failure before a compensatory mechanism can be established

A particular finding occasionally seen in mitral disease is an enormous enlargement of the left atrium. It is not alone the degree of stenosis that accounts for such cases but rather the combined effect of mitral regurgitation, mitral stenosis, the dilatation that comes with atrial fibrillation, acute rheumatic involvement of the myocardium of the left atrium, and other factors not well understood, perhaps an active circulation or sometimes pericardial adhesions over the left atrium. In a series of 26 cases of very large left atria found at autopsy at the Massachusetts General Hospital, 16 showed mitral stenosis and 10 mitral valve deformity (causing regurgitation) without stenosis, which indicates that structural mitral regurgitation is by no means an innocuous condition.

The heart muscle in mitral valve disease may be normal except for hypertrophy. With acute endocarditis there are often acute inflammatory myocardial reactions like the Aschoff bodies in the rheumatic infection, but with chronic healed valvular disease there need not be any trace of previous infection in the perfectly healthy muscle. Eventually the myocardium may become exhausted and fail without evidence of pathologic change unless there is a complication such as acute rheumatic infection or serious coronary disease. Thus it is at times the valve lesion and not myocardial disease that eventually causes failure and death, although it is equally true that active infection, especially recurrent rheumatism or some other complication, proves too great a burden for the heart that is already overloaded. In recent years there has been too great a tendency to blame the heart muscle entirely and to exaggerate the valve lesion. This is a limited point of view although it has been helpful in calling attention to the fact that mitral insufficiency is often the result of heart failure or dilatation and not its cause. In the process of this demonstration the pendulum has swung too far. The truth rests between the extreme points of view.

The effects of mitral valve disease on organs of the body other than the heart vary with the degree of involvement of the valve and with the occurrence of complications. The only direct effect is on the pulmonary circulation which becomes engorged; the small arteries and capillaries are seriously affected with marked dilatation and thickened walls resulting in great difficulty in the transfer of oxygen and carbon dioxide from the limited inspired air to blood stream and vice versa (Parker and Weiss, 1936). There develops a steadily increasing pulmonary arterial pressure when either stenosis or regurgitation of the mitral valve is at all pronounced. All this leads naturally to a diminution in air space and vital capacity and to a tendency to bleeding or effusion of serum (edema) into the interstitial tissue and into alveoli and bronchioles. There slowly develops also an extensive interstitial fibrosis with enormous thickening of the alveolar walls to resemble eventually the picture of "mahogany" pulmonary sclerosis due to other causes. Also in time in cases of

chronic mitral stenosis there may be laid down in the lung tissue iron deposits from the infiltration of blood and these deposits may give rise to a characteristic x ray picture of miliary pulmonary hemosiderosis. The liver becomes congested only when the right heart fails but such congestion over the years may lead to a moderate cardiac cirrhosis of the liver.

**Symptoms** There are no symptoms of mitral valve disease except for evidence of the limited air space in the lungs in most cases. Dyspnea on effort is common when the mitral valve disease is more than slight in degree while indication of a high degree of pulmonary engorgement from marked mitral stenosis is dyspnea even at rest or in paroxysmal attacks (with or without acute pulmonary edema or cardiac asthma) when the heart rate suddenly increases. The dyspnea in mitral stenosis is not to be attributed to failure of the myocardium it is due to the mechanical effect of the stenosed mitral valve. Cough and hoarseness due to the pressure from a very large left atrium are uncommon symptoms as is also hemoptysis due to pulmonary apoplexy.

Vioussens R. *Traite Nouveau de la Structure et des Causes du Mouvement Naturel du Coeur*. Jean Guilleminet. Toulouse 1715 pp 105 and 106 (Translation by myself)

I perceived that the opening into the left ventricle appeared very small and was of an oblong oval shape and in seeking the cause of such a surprising fact I discovered that the cusps of the mitral valve were truly bony and so thickened and contracted that they very much narrowed the ostium.

The entrance into the left ventricle having been much narrowed and its margin having lost all its natural suppleness the blood could no longer enter so freely and abundantly as would be necessary into the cavity of this ventricle in consequence of the embarrassment of the circulation the blood began to dilate extraordinarily the trunk of the pulmonary vein [that is the left atrium] because it remained there so long and collected in such a great quantity. The blood had no sooner begun to make too long a stay in the main trunk of this vein than it delayed the course of blood in all the blood vessels of the lung so that the branches of the pulmonary artery and vein extending throughout all the tissues of the lung were always too much filled with blood and consequently so dilated that they compressed the vesicles to such an extent as to hinder the air from entering and leaving freely *that is why the patient breathed always with much difficulty* (Italics mine)

Complications like congestive heart failure, atrial fibrillation, pulmonary embolism, massive left atrial enlargement, and acute rheumatic or bacterial endocarditis may produce symptoms which are discussed in the chapters in this book dealing with these subjects. Angina pectoris in mitral stenosis is rare having been found in only 2.6 per cent of Levine and Kauver's 741 cases (1942) and then almost always due to an incidental complication of coronary heart disease. There were however three of these authors' cases of mitral stenosis with angina pectoris who showed no significant coronary artery disease and these plus a few others seen by ourselves and by other observers (Blackford 1940, Dressler 1942) indicate the probability that in rare cases

of marked mitral stenosis the output of blood from the heart may be inadequate to meet the needs of the coronary circulation on effort

**Signs** There are only two pathognomonic signs of mitral valve disease one auscultatory and the other roentgenologic Both show the presence of mitral stenosis Mitral regurgitation due to valvular disease cannot be easily differentiated from mitral regurgitation due to ventricular dilatation except when it is combined with proof of mitral stenosis

The auscultatory proof of mitral stenosis is the presence of a rumbling apical middiastolic murmur (Figure 15, page 95) with or without presystolic accentuation in the absence of considerable aortic regurgitation or other cause of left ventricular dilatation It was first recognized by C J B Williams more than a century ago but his description went unheeded until the present generation again called attention to it as an essentially diastolic and not merely a presystolic murmur

Williams C J B *Diseases of the Chest* John Churchill Publisher London 3d edition 1835 p 198

**Mitral valve** Obstructive disease of this valve commonly consists in an adhesion together or ossification or rigidity of some of its parts or in a thickening and contraction of the fibrous ring at its base It may cause a murmur with the diastole of the ventricle and therefore at the time of the 2nd sound for although the ventricle in itself produces no sound yet when the orifice by which it becomes refilled is contracted the current being partially resisted in passing through may become sonorous This will therefore leave the result much as Laennec represented it inasmuch as there is a current from the auricles to the ventricles during the diastole of the latter although this current is not produced as he supposed, by the contraction of the auricles But the results of my late experiments must modify the statements of both M Laennec and Dr Hope in this respect that the contraction of the mitral orifice with its impeded current and attendant murmur will not necessarily supplant the 2nd sound inasmuch as this sound is seated in the semilunar valves the action of which may still be perfect

The roentgenologic proof of mitral stenosis is the presence of a considerable increase in the size of the shadows of the right ventricle and of the pulmonary artery combined with well marked enlargement of the left atrial shadow, or the latter finding with any type of ventricular enlargement left right or combined (Figure 127) Given either or both of these auscultatory and roentgenologic findings and they are usually combined the presence of a apical systolic murmur means mitral regurgitation as well as mitral stenosis and is due to the valvular disease (provided a respiratory murmur can be excluded) A large left atrium raises the left bronchus

Other signs strongly suggesting though not proving mitral disease include a loud apical systolic murmur without any diastolic murmur in the absence of any acute or subacute illness or of evidence of left ventricular enlargement Appreciable left ventricular enlargement would of course indicate that the cause of such a murmur could well be ventricular dilatation The history of



FIG 17 Roentgenograms showing a heart with a high degree of mitral stenosis a big right ventricle and marked enlargement of the left atrium which bulges to the right above the right atrium in the anteroposterior view (A) and posteriorly into the shadow of the spine in the right anterior oblique view (B) Note the displacement of the barium filled esophagus by the broad curve of the left atrium below the aortic and pulmonary artery notches in the oblique view

rheumatic infection in the past makes this apical systolic murmur all the more important evidence of mitral disease

Another corroborative sign of mitral disease is accentuation of the first heart sound at the apex which as Cossio has shown (1943) may be delayed in relation to the onset of systole (due to the hemodynamic conditions present) and preceded by a short period of systolic vibration which may or may not be in turn preceded by a true presystolic murmur. Less important corroborative signs are accentuation of the second sound at the pulmonary area, the presence of atrial fibrillation under the age of forty years, increased prominence of the left upper border of percussion dullness or roentgen ray shadow and increased width and depth of the lung hilus shadows by roentgen ray (due to the dilatation of the pulmonary blood vessels)

A diastolic thrill limited to the apex merely accompanies a marked mitral diastolic murmur

Another strongly suggestive and practically pathognomonic sign of mitral disease is the electrocardiographic evidence of abnormal right ventricular preponderance combined with atrial fibrillation. The abnormal right ventricular preponderance alone with normal rhythm and increased atrial or P waves is found also in congenital pulmonary stenosis or interatrial septal defect but with a rheumatic history and a systolic murmur limited to the apex it strongly favors mitral valve disease. The occurrence of atrial fibrillation with abnormal right ventricular preponderance is rare in congenital heart disease and common in mitral disease (Figures 128 and 129)

The blood pressure is of no importance in the diagnosis of mitral disease. It may be normal, low, or high. A low systolic pressure with small pulse pressure is common but hypertension of the essential type is a not infrequent complication even in well marked mitral stenosis.

Other signs found with mitral disease are merely those due to various complications.

**Course and prognosis.** The chief cause of chronic crippling of the heart in young adults is extensive mitral disease of rheumatic type. Lesser grades of mitral stenosis or regurgitation or of both combined often permit long lives with relatively little crippling.

The course and prognosis of mitral disease vary according to the extent of the lesion, the etiologic factors, and the complications. The lesion may be so slight that there is little or no deformity of the valve with little or no stenosis or regurgitation. In such cases the course is that of a person with a normal heart and the prognosis is excellent with but one exception which is however important. A damaged mitral valve, whether or not discovered clinically, is a liability in that it is much more frequently than is a normal valve the site of repeated rheumatic infection in youth and if there is not much mitral stenosis of bacterial endocarditis in youth and middle age.

If there is marked and preponderant stenosis of the mitral valve in youth the victim develops symptoms and signs of diminished cardiac reserve and frequently of atrial fibrillation (in over one half of the cases) and dies usually

of congestive failure due to right ventricular exhaustion in young adult life or middle age especially in the presence of a recurrent rheumatic infection or pulmonary infarction. The high pressure in the pulmonary circulation occasionally results in bleeding slight as shown by bloodstained sputum or extensive with hemoptysis. Occasionally complications like pericarditis or cerebral embolism from intra atrial thrombosis in the cases with atrial fibrillation hasten death. The duration of life after the establishment of well marked mitral stenosis averages ten to twenty years but occasional cases far exceed this length of time while other cases die within a few months to a year or

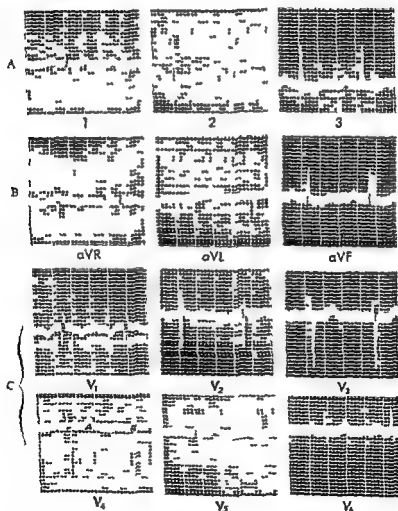


FIG. 128. Electrocardiogram in a case of mitral stenosis showing normal rhythm, female, age 45. (A) Bipolar limb leads 1, 2, and 3. (B) unipolar limb leads aVR, aVL, and aVF. (C) six precordial leads  $V_1$  to  $V_6$  inclusive. Note right axis deviation in limb leads and wide P waves. Time = 0.04 and 0.20 second; amplitude 1 mm = 0.10 mv.



two In the last edition of this book I noted that four cases of moderate degrees of rheumatic mitral stenosis exceeding the age of 80 years and proved at autopsy had come to my notice (White and Bland 1941) in one of the four namely Dr Herman F Vickery there had never been any cardiac symptoms during a very active life until angina pectoris on effort due largely or wholly to coronary heart disease developed at the age of 77 years At autopsy after death from pneumonia in his eighty fourth year the heart was

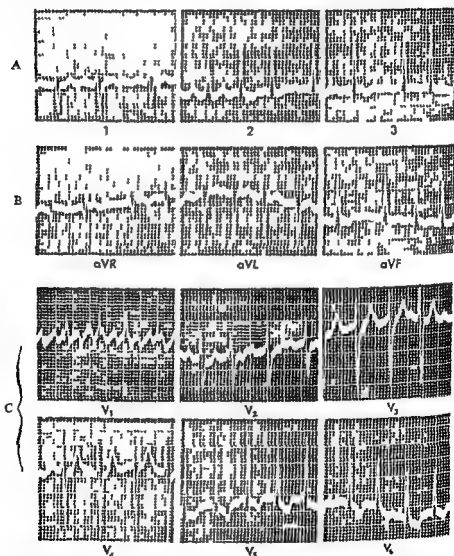


FIG 129 Electrocardiogram in a case of mitral stenosis showing coarse atrial fibrillation and right axis deviation female age 88 (A) Bipolar limb leads 1 2 and 3 (B) unipolar limb leads aVR aVL and aVF (C) six precordial leads V1 to V6 inclusive. Note also the regular rapid atrial action (450 per minute) resembling flutter in Lead V1. Time = 0.04 and 0.20 second amplitude 1 mm = 0.10 mv

but slightly heavier than normal and the left atrium was very little if at all enlarged (the heart rhythm had been normal) Since 1941 I have encountered several more very old persons with rheumatic mitral stenosis

Marked mitral regurgitation is a greater strain on the heart than is mitral stenosis and life is shorter usually lasting but a few years at best It should be emphasized again that the degree of mitral regurgitation is indicated roughly by the intensity of the apical systolic murmur in that the murmur is loudest, other things being equal when the regurgitation is moderate and faintest when the regurgitation is only very slight or else of extreme degree as discussed in Chapter 5 If the mitral ostium remains wide open during systole there should be no mitral systolic murmur at all such a possibility is however remote

**Complications** The commonest complications of mitral disease have already been mentioned (1) pulmonary congestion without heart failure (2) right ventricular failure (3) atrial fibrillation and (4) pulmonary embolism with infarction. Pulmonary congestion is especially common and slight bleeding from this or very rarely brisk hemoptysis from rupture of a larger pulmonary blood vessel (pulmonary apoplexy) may occur Sudden flooding of the pulmonary circulation in mitral stenosis by overactivity of the strong right ventricle due to tachycardia from effort or excitement or paroxysmally occasionally precipitates a paroxysm of dyspnea which may or may not be asthmatic (one type of cardiac asthma—McGinn and White 1934)

However it is very important not to confuse this picture of pulmonary congestion with that of pulmonary embolism with infarction which is also a common complication of mitral stenosis and one often disregarded or overlooked (Levine and White 1937) an unrecognized venous thrombosis especially in the leg of a patient with mitral stenosis and congestive failure is more often responsible for such pulmonary embolism than is an intracardiac thrombus in the right heart chambers and is of course more amenable to treatment (by ligation) The thrombosis may be concealed in a leg already swollen in congestive heart failure and the pulmonary infarction may be concealed by congestive rales or hydrothorax in such a case but unexplained fever leukocytosis tachycardia and sometimes hemoptysis and jaundice are clues calling attention to this complication

Congestion of the liver due to stasis in the right heart chambers and inferior vena cava with particular effect on the low pressure in the hepatic veins is frequent. After years of such hepatic congestion liver atrophy is found along with areas of regeneration and finally a real cirrhosis may develop with ascites out of proportion to the degree of dependent edema Intra atrial thrombosis rarely of the ball type loose in the atrium sometimes occurs in mitral disease (more often in the cases showing atrial fibrillation) pieces of such thrombi may be thrown off to brain kidneys spleen or extremities as aseptic emboli A ball thrombus may rarely block the circulation completely but transiently with evidence of such obstruction in the peripheral circulation (absent pulses cadaveric discoloration of fingers and toes) and brain. Marked

enlargement of the heart chambers especially of the left atrium may cause pressure symptoms and signs in the thorax such as cough and very rarely recurrent laryngeal nerve paralysis (produced probably by pressure from the pulmonary artery pushed up against the aortic arch by the enlarged left atrium) Recurrent rheumatic infection is common in the younger cases and subacute bacterial endocarditis is an occasional fatal complication Apparently valvular stenosis protects somewhat against *Streptococcus viridans* endocarditis probably through failure of the valve to close in systole there no longer being the factor of trauma at the valve line of closure to favor the lodgment of the bacteria Angina pectoris rarely complicates mitral stenosis (see comment under Symptoms)

Rupture of the mitral valve may occur when inflamed or from trauma and rupture of the chordae tendineae which may lead to serious mitral regurgitation and congestive heart failure (Bailey and Hickam 1944)

Other types of heart disease thyroid hypertensive and coronary are at times associated with mitral valve disease syphilitic aortitis is rarely a complication Other valve lesions are often found with mitral valve disease especially those of the aortic valve A variable degree of tricuspid valve disease is found in about one quarter of all cases of mitral valve involvement percentages of 15 up to 40 have been reported An interesting complication of mitral stenosis is congenital deficiency of the atrial septum discussed in Chapter 13 the septal defect diverts blood into the right atrium probably almost doubling the load on the pulmonary circulation and resulting in much greater enlargement of the right heart chambers than of left

Neurocirculatory asthenia and cardiac neurosis frequently complicate mitral disease the latter particularly as the result of exaggeration of the importance of heart murmurs by the physician Various other illnesses and infections and diseases of other organs may occur but tuberculosis of the lungs is infrequently found in the presence of marked mitral stenosis

**Treatment** In the last edition of this book (1944) I stated that there was no specific therapy for mitral valve disease that complications must be treated as such and that the life of a person with mitral disease should be somewhat protected especially against heart failure and against infection of rheumatic and subacute bacterial nature but during the last few years progress has been made in two directions both surgical An ingenious and successful anastomosis between one of the right pulmonary veins and the vena azygos has been carried out in several cases of tight mitral stenosis to prevent recurrent attacks of severe acute pulmonary edema through the establishment of a safety valve (Bland and Sweet 1949) an atrial septal defect has been produced for the same purpose (Harken Ellis et al 1948) The other procedure has been the evolution of more promising plastic surgery on the deformed valve itself (Bailey et al 1949 Harken 1950 and others) than the pioneer efforts of Cutler which had to be abandoned because of a very high mortality over twenty years ago (Cutler and Beck 1929) The best technique now (early in 1951) is the incision or rupture of the cusp adhesions at the

commissures The next decade may be a crucial one of further progress in valvular surgery but of far greater importance of course will be efforts also beginning to look promising to control the chief cause of valvular deformity namely rheumatic fever itself

**Differential diagnosis** Mitral valve disease must be primarily differentiated from functional mitral regurgitation from respiratory systolic murmurs from relative mitral stenosis in cases of left ventricular dilatation with or without aortic regurgitation from transmitted murmurs of aortic stenosis of tricuspid stenosis and of congenital defects (pulmonary stenosis and interventricular septal defects) and from the overactive heart in thyrotoxicosis or neurocirculatory asthenia The signs whereby this differentiation may be made have already been discussed here I would simply reiterate that with considerable cardiac enlargement it is sometimes impossible to distinguish by clinical examination mitral valvular disease from the manifestations of left ventricular dilatation Finally it should be said that occasionally mitral disease even of extensive degree may exist without proof of its existence especially when the heart action is weak the heart very large or some overshadowing complication present

## B AORTIC VALVE DISEASE

Aortic valve disease is generally considered to be more serious than mitral valve disease The chief reason for this is that aortic valve disease is often caused by a neglected syphilitic infection Moreover slight degrees of involvement are frequently missed in diagnosis the soft aortic diastolic murmur being unheard and the systolic murmur of slight aortic stenosis unattended by a thrill being disregarded because of the absence of all other signs As a matter of fact disease of the aortic valve is often of very slight degree and when it results from a rheumatic infection in youth it may be compatible with a long and fully active life

**Etiology Cause** The cause of aortic valve disease is commonly either rheumatic or syphilitic the former occurring more often in such parts of the world as New England where the rheumatic infection is common and the latter more often in regions where syphilis is more frequent and rheumatism relatively infrequent Other causes of aortic valve disease are relatively rare and consist of bacterial endocarditis collagen diseases and sclerosis The valve ring itself may be stretched with or without any lesion of the valve cusps this fact explains the aortic regurgitation in certain cases of syphilitic aortitis or of chronic hypertension especially when aortitis and hypertension are combined and in rare cases of severe anemia in a series of 200 consecutive autopsied cases of hypertensive heart disease with normal aortic valves an aortic diastolic murmur had been found in 14 i.e. 7 per cent (Garvin 1940) Trauma is a very uncommon cause of aortic valve lesions it occurs particularly in the case of a valve already damaged Congenital aortic valve defects are infrequently found the bicuspid valve is the commonest

**Age** The age at which aortic valve disease is present extends from early childhood to extreme old age. It is commonest in middle age when the rheumatic aortic valve lesion is still encountered, the syphilitic lesion most frequent, and the sclerotic type beginning to appear.

**Sex** The male sex shows much more aortic valve disease than does the female sex, in about the ratio of 3 to 1. This is due not only to the fact that syphilitic aortitis is much more common in the male, but also to the fact that the rheumatic infection involves the aortic valve more often in the male and that sclerotic changes are also more common in that sex.

**Pathology** The pathology of aortic valve disease depends on the etiological factor. Active inflammation of the valve has already been discussed at the beginning of this chapter and in Chapters 14, 15, and 16. It remains to discuss the chronic deformities of the valve and their effect on the heart and aorta.

(a) A single mild *rheumatic* valvulitis may leave no deformity, but severe or repeated infections tend to cripple the valve through adhesion of the cusps at their commissures, thereby producing stenosis of various degrees, or through scarring, retraction, and stiffening of the free borders of the cusps, thereby producing regurgitation. As in the case of the mitral valve, so here too the rheumatic lesion usually causes both stenosis and regurgitation, giving rise rarely to regurgitation alone, except in the earliest stages, and also rarely to stenosis alone. There are varying ratios of stenosis and of regurgitation in different cases and during the evolution of a single case. The end result of a rheumatic lesion or of repeated rheumatic lesions may be either preponderant aortic stenosis (Figure 130), preponderant aortic regurgitation, or equal grades of both. From the clinical standpoint it is useful to attempt to make this differentiation. Preponderant regurgitation is much more common than preponderant stenosis, in the ratio of about 5 to 1, but in New England pure aortic regurgitation as determined at postmortem examination is less common than the combination of aortic stenosis and regurgitation. In Cabot's series (1926) there were 93 cases showing stenosis and regurgitation of the aortic valve and 55 cases showing regurgitation with little or no stenosis, which gives a proportion of 148 instances of aortic regurgitation to 93 of aortic stenosis. The healed rheumatic aortic valve may become calcified and stony, especially when there is marked stenosis.

(b) In *subacute and acute bacterial endocarditis* the vegetations may be so large that they cause actual stenosis, or increase it if stenosis is already present; they may even project upward from the cusps and block the mouths of the coronary arteries. There may be extensive ulceration of the valve cusps with rupture, or the development of small aneurysms of the sinuses of Valsalva. Usually bacterial endocarditis is superimposed on an aortic valve previously damaged by rheumatic infection, or on a congenitally abnormal valve (bicuspid especially), but it may attack a normal valve, and in the early stages, as in the case of the rheumatic lesion, there may be no deformity. Permanent deformity may result, consisting of stenosis, regurgitation, or both, with a tendency to calcification of the damaged valve.

(c) As the result of *syphilitic* involvement the commissures of the aortic valve become permanently widened to cause regurgitation (Figure 131) The aortic valve ring also may be dilated with the development of extensive regurgitation Aortic stenosis is not the result of syphilis itself although rarely in healed cases complicating calcification or subacute bacterial endocarditis may cause some degree of stenosis

(d) The *sclerotic* lesion of the aortic valve found as a primary condition in older individuals (Monckeberg 1904) is not commonly of a degree sufficient to cause much deformity of the valve It is a different process from that of secondary calcification of rheumatic or other types of infectious endocarditis although they may exist together The sclerotic lesion is a subendocardial process beginning as atheroma and progressing to calcification especially at the base of the valve as it increases it grows into the valve cusps stiffening and deforming them first at their bases and producing a slight aortic stenosis This kind of aortic stenosis probably accounts for an aortic systolic murmur in some elderly individuals in whom there is no evidence of aortic dilatation a diagnosis of aortic dilatation has at times been made unjustifiably to explain an aortic systolic murmur of obscure origin When the whole valve is involved and a stony mass projects into the aortic lumen



FIG 130 Photograph showing marked aortic stenosis Bicuspid valve (kindness of Dr Ronald Grant Guy's Hospital London)

resulting in well marked aortic stenosis Monckeberg's sclerosis alone usually is not to blame but rather a combination of an old infectious process and superimposed calcification In a series of 40 cases of calcific sclerosis of the aortic valve studied microscopically with care only 3 cases were thought to fit pure Monckeberg's sclerosis of the remaining 37 18 were clearly rheumatic in origin and another 19 probably so (Karsner and Koletsky 1940) The endocardium may be eroded just as the endothelium in the aorta is at times eroded over calcified plaques

(e) Serious *congenital* aortic valve lesions stenosis and atresia are very rare but congenital bicuspid aortic valves are found occasionally and are likely to be the site of subacute bacterial endocarditis quadricuspid aortic



FIG 131 Syphilitic aortitis and aortic insufficiency The aortic valves are thickened and rolled at their margins and widely separated at the commissures The coronary mouths are obliterated Note wrinkling and stellate scarring of aortic intima The left ventricle is dilated and the trabeculae carneae flattened—evidence of aortic regurgitation (W G MacCallum *A Text Book of Pathology* 1928 Kindness of W B Saunders Company Philadelphia)

valves are seldom encountered Subaortic stenosis involving the infundibulum (outflow tract) of the left ventricle is more often found as a congenital defect than stenosis of the valve itself but both are rare

(f) *Rupture* Blows and very rarely indirect strain may cause linear ruptures of the aortic cusps at their bases or through their structure anywhere even when no disease is present probably due to a high pressure effect at the moment of valve closure associated with inferiority of tissue strength Almost invariably however lesions due to acute or subacute bacterial endocarditis or to syphilis are the cause of weakening of the valve before rupture takes place When there is some such disease present no definite trauma is needed to cause rupture, ordinary cardiac action being sufficient

Normally in the adult the aortic valve ring circumference measures 7 to 8 cm if it measures 5 cm or less the stenosis is marked enough to be of considerable clinical importance and should be clinically diagnosable

*Effect of aortic valve disease on the heart* The effect of aortic valve disease on the heart itself is very variable There may be no evident effect when there is no valve deformity or when there is very slight regurgitation or stenosis Marked *aortic regurgitation* has a more rapidly serious effect than has marked aortic stenosis The heart becomes very large with the apparently simultaneous development of left ventricular hypertrophy and compensatory dilatation producing eventually the *cor bovinum* the ox heart which may weigh as much as 1 000 gm or more and which is as a rule widely dilated The heart of pure aortic regurgitation is on the average the heaviest and largest known It is most often seen in syphilitic aortitis but occasionally it results from the rheumatic infection When the left ventricular dilatation in aortic regurgitation reaches a certain degree the mitral valve no longer remains competent and left atrial enlargement (dilatation and hypertrophy) ensues followed in turn by right ventricular enlargement and eventually by right atrial enlargement too though death due to left ventricular failure is likely to interrupt the full evolution of these various steps Pulmonary congestion occurs after the left ventricle has begun to fail

The heart muscle may be unaffected in cases of marked aortic regurgitation other than to show great hypertrophy and to be stretched around a widely dilated left ventricular cavity with flattened trabeculae Thus strong and seemingly healthy muscle may fail under the strain of the overwork which is caused by the valve lesion abetted by defective coronary circulation which in turn is the result of the low diastolic blood pressure Normally it is a sufficient blood pressure in diastole that maintains the coronary circulation at a proper level Although narrowing of the coronary artery mouths by the aortitis so often accompanying aortic regurgitation may still further weaken the myocardium actual pathologic changes in the myocardium are only infrequently seen when such changes do occur they result from concurrent occlusion or much sclerotic narrowing of the coronary arteries or from rheumatic myocarditis if there is an active rheumatic infection

Marked *aortic stenosis* generally of gradual development causes steadily



increasing hypertrophy of the left ventricle with little or no dilatation until the heart begins to fail. The hypertrophy is of the concentric type as compared with the eccentric type in aortic regurgitation and the heart remains relatively small in bulk although considerably increased in weight. Eventually the heart in aortic stenosis may become two or three times the normal weight but this occurs much more readily if considerable aortic regurgitation is also present. The other heart chambers are unaffected in aortic stenosis until the left ventricle fails. It is surprising to discover how well aortic stenosis may be borne even by old persons and yet it must be considered a constant strain on the left ventricle and a possible cause of sudden death. Congenital subaortic stenosis acts on the heart much as does acquired aortic stenosis itself.

*Effect of aortic valve disease on the aorta.* Aortic dilatation is commonly found with marked aortic regurgitation especially when the aorta is the seat of a syphilitic process with loss of its elasticity and muscular continuity even with rheumatic aortic regurgitation the aorta becomes somewhat stretched but not so much permanently as temporarily with each systole. In cases of preponderant aortic stenosis the aorta may be normal in caliber and in other respects also.

**Symptoms.** The only symptoms of aortic valve disease itself are a tendency to faintness, dizziness or even syncope in patients with marked aortic stenosis and to throbbing, forceful pulsation of heart and arteries in patients with marked aortic regurgitation. In advanced cases it is common to find symptoms of left ventricular failure such as paroxysmal dyspnea with or without cardiac asthma and of coronary insufficiency (angina pectoris) without other cause than the aortic valve disease. In some young individuals usually of nervous type, aortic regurgitation especially when marked in degree is attended by paroxysmal angina pectoris and hypertension even at rest.

**Signs.** The early stage of acute rheumatic aortic valve involvement and even the chronic aortic valve lesion too may be so slight in degree that there is no valve deformity and therefore no sign of disease of the valve. The same is true of acute bacterial endocarditis of syphilitic invasion and of sclerotic change in their earliest stages but when the valve is deformed there are always signs of its affection except in moribund conditions. The clinical proof of aortic valve disease rests primarily on auscultatory findings.

*Aortic stenosis* when very slight is without signs or attended by only a minimal systolic murmur when of moderate degree it is accompanied by a loud systolic murmur in the second intercostal space just to the right of the sternum with or without a slight palpable thrill and with slight to moderate cardiac enlargement of the left ventricular type. When the stenosis is of considerable degree the aortic systolic murmur is very harsh and widely transmitted especially along the great vessels toward neck and arms and even into the abdominal aorta the aortic systolic thrill is marked the second aortic sound is often absent the heart is considerably enlarged and the peripheral pulse is small and often of plateau or anacrotic type with low systolic and small pulse pressure (see Chapter 8).

The triad of murmur thrill and small pulse is the essential finding the other findings are corroborative. It is not necessary however to wait for an aortic systolic thrill or a plateau pulse to make a diagnosis of aortic stenosis the diagnosis can be made on the aortic systolic murmur alone in a patient without aortic dilatation or hypertension provided the murmur is loud and harsh. Accuracy of diagnosis has increased greatly in our hands since we have made this change in the diagnostic criteria of aortic stenosis. It is furthermore of great interest to remember that the systolic murmur of aortic stenosis is well transmitted to the cardiac apex but not to the lung bases in back while the systolic murmur of mitral regurgitation is well transmitted to the lung bases in back but not to the base of the heart. The heart rhythm is usually normal in aortic stenosis.

There is a characteristic roentgen ray picture of the heart somewhat enlarged by the presence of relatively uncomplicated aortic stenosis (without hypertension or myocardial failure and with little or no aortic regurgitation) there is a compact concentric enlargement of the left ventricle without increase of pulmonary artery and with little aortic prominence (Figure 132). The electrocardiogram in time develops the pattern of left ventricular enlargement (high R waves and depressed or inverted T waves in Lead I and in the pre-cordial leads over the left ventricle  $V_4$ ,  $V_5$  and  $V_6$ ) (Figure 133 page 691) as in the case of the hypertensive heart (see Figure 97, page 477).

The signs of congenital subaortic stenosis are essentially the same as those of acquired aortic stenosis.

*Aortic regurgitation* is shown by the presence of an early blowing diastolic murmur heard maximally along the left sternal border over the sternum itself at the level of the second and third ribs or in the second intercostal space just to the right of the sternum provided one can rule out pulmonary regurgitation which is a very rare valve defect. Pulmonary regurgitation can almost invariably be excluded by the absence of marked mitral stenosis (which is the usual factor behind pulmonary regurgitation) and by the absence of the very rare congenital or acquired pulmonary valve disease with regurgitation.

The heart may not be found appreciably enlarged on either physical or roentgenologic examination in the presence of a slight degree of aortic regurgitation which is sufficient nevertheless to give a characteristic murmur nor need there be in such cases any abnormality of blood pressure or of the character of the peripheral pulse. Cardiac enlargement particularly of left ventricular type is readily found by any method of study in the presence of considerable aortic regurgitation associated with such enlargement are a full pulse pressure due to a low diastolic pressure (often as low as 30 or 40 mm of mercury and sometimes not measurable above zero) a water hammer pulse capillary pulse in very rare cases even pulsation of the spleen a double murmur in the great arteries when compressed (Duroziez's sign Duroziez 1861) and a double murmur at the base of the heart. The roentgen ray in such cases besides showing the left ventricular enlargement (Figure 132)

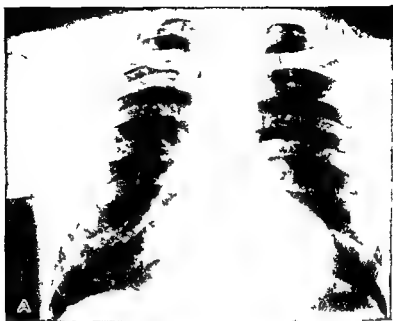


FIG 132 Roentgenograms of the thorax in two cases of aortic valve disease (A) stenosis (B) regurgitation Both young men (kindness of Dr Hugo Roesler Temple University Philadelphia)



FIG 133 Electrocardiogram in a case of aortic stenosis with enlargement of the left ventricle. Male age 59 (A) Bipolar limb leads I, II and III (B) unipolar limb leads aVR, aVL and aVF (C) six precordial leads V1 to V6 inclusive. Note especially the deep S wave in Leads V1 to V3 inclusive and the high R waves and inverted T waves in Leads I, II, V4 and V5. Time = 0.04 and 0.20 second; amplitude 1 mm = 0.10 mv.

usually reveals a full ventricular pulse with increased pulsation in the aorta. The electrocardiogram usually shows abnormal left ventricular preponderance with high *R* waves and inversion of the *T* waves in Leads 1, *V*<sub>1</sub>, *V*<sub>2</sub> and *V*<sub>3</sub> in these marked cases very similar to the record in marked aortic stenosis (see Figure 133 page 691). If we wait however for all the confirmatory signs of marked aortic regurgitation before making the diagnosis we shall miss about half of the cases namely, those in which the lesion is too slight to give more than the characteristic murmur and perhaps a little cardiac enlargement.

A combination of aortic stenosis and aortic regurgitation gives signs mid way between the extreme signs of the individual defects.

**Course and prognosis** Slight grades of aortic valve disease of rheumatic origin appearing in youth and sometimes discovered accidentally on routine examination are often well supported without symptoms during long and active lives. Such lesions are however always a menace because of the possibility of recurrent rheumatic infection with more definite crippling or of bacterial endocarditis superimposed on the valve already damaged. Marked aortic regurgitation is always a serious burden and if it is of syphilitic origin it may not permit more than a few years of life. Although marked aortic stenosis is also an important burden it is a lighter one than marked aortic regurgitation in part because an active syphilitic process is not a factor in some cases it may limit the duration and activity of life relatively little and I have found the gradual development of aortic stenosis over a period of years a good omen in a young adult who starts off with a considerable degree of rheumatic aortic regurgitation. However in either case regurgitation or stenosis the less the physical strain or frequency of infection the longer the life. Congestive heart failure and angina pectoris are frequent causes of death in aortic valve disease. Also unexplained syncope and sudden death are not rare in aortic stenosis of high degree. Sudden death in aortic stenosis was first recorded by Bonetus in 1679 (see below) it occurred in 18 per cent of 100 cases of calcareous aortic stenosis analyzed by Horan and Barnes (1948). When congestive failure first appears in either aortic stenosis or aortic regurgitation it is difficult to control recurs quickly and indicates usually a short survival of a few months to a year or two.

Bonet T *Sepulchretum sive Anatomia Practica* Leonard Chouet Geneva 1679  
Vol I Book II Section XI (De morte repentina on sudden death) Observa-  
tion XXVI (Translation my own)

*Anatomy of a man who died suddenly and whose semilunar valves situated at the mouth of the aorta were turned to bone*

A Parisian tailor residing in the district of St James full blooded and inclined to obesity and not yet old having dined and left his house had walked hardly 40 paces when he suddenly fell to the ground and expired.

Carried back to his home his body was opened and no disease was found anywhere except that the three semilunar cusps situated at the entrance of the aorta from the left ventricle were discovered to be bony. I received one of these as a

gift and found it of whitish color and so hard that it could hardly be incised with a knife

**Complications** Aside from the complications of mitral valve disease congestive failure angina pectoris and subacute bacterial endocarditis in aortic valve disease other direct associations are rare For instance atrial fibrillation is infrequent and hypertension is not very common Coronary disease of high degree is however sometimes found as is also neurocirculatory asthenia and it is important to note that the blood pressure may be quite high even in the presence of marked aortic stenosis

**Treatment** There is as yet (1950) no adequate reparative treatment for aortic valve disease itself although much promising research is in progress with respect both to plastic surgery and to artificial valves \* however the etiologic factors—syphilis and rheumatism—should be treated if they are still active Congestive failure and angina pectoris should receive therapy as such without regard to the valvular disease

The discovery of aortic valve disease even of slight extent demands some consideration it should neither be exaggerated nor underrated The individual should not be made into a neurotic cripple on the other hand he should be given an intelligent explanation of his trouble and advised to protect himself against strenuous exertion or fatigue Foci of infection should be eradicated and respiratory infections should particularly be avoided Penicillin should be administered at the time of dental extractions to give protection against subacute bacterial endocarditis

**Differential diagnosis** Aortic valve disease must be differentiated from functional aortic regurgitation pulmonary regurgitation pulmonary stenosis patent ductus arteriosus interventricular septal defect aortic dilatation or aneurysm a venous hum in the neck transmitted to upper chest and marked peripheral vasodilatation The differentiation is generally easy the commonest errors are in confusing dilatation of the aorta with aortic stenosis and in overlooking slight aortic regurgitation The discussion above of the signs in aortic valve disease covers the differential points It may be impossible to distinguish aortic regurgitation due to valvular disease from that of functional type the latter is so much less common however that it is generally safest to disregard the possibility of its occurrence in an individual case except in severe anemia or in a case of chronic hypertension with variable aortic diastolic murmur As a rule when functional aortic regurgitation is diagnosed clinically it is found at postmortem examination that aortic valve disease is present The greatest problem of all lies in the differential diagnosis of etiologic factors behind aortic regurgitation sometimes this problem is insoluble during life despite careful study and even postmortem examination may fail to give the answer

### C TRICUSPID VALVE DISEASE

Tricuspid valve disease has been of very little clinical importance as compared with disease of the mitral aortic and even of the pulmonary valves

Most recently (autumn 1951) surgical approach to the problem by dilatation of the stenosed aortic valve is being explored by Bailey of Philadelphia.

The reasons for this are three. In the first place deformity of the valve sufficient to be of clinical significance is rare. Secondly, when such deformity is present it is usually overshadowed by a higher and much more important degree of mitral valve disease. And thirdly except in rare instances tricuspid valve disease has not been diagnosed ante mortem though it has been sometimes suspected. Recently however there has been an improvement in the accuracy of diagnosis as witness a 34 per cent correct diagnosis in fifty cases of tricuspid stenosis found among 150 patients with rheumatic heart disease studied post mortem (Aceves and Carral 1947).

Tricuspid valve disease rarely occurs without other valve lesions. In a series of 173 cases (Osler and Gibson 1915 including for the most part cases originally collected by Leudet 1888) tricuspid stenosis is said to have been found alone in only 12 and in all these 12 the lesion was apparently of congenital origin. In 158 there was also a mitral lesion further complicated by an aortic valve lesion in 58 and by a pulmonary valve lesion in 3. In 3 cases the tricuspid and pulmonary valves were involved. None of the 30 cases of tricuspid stenosis personally observed by Dressler and Fischer (1929) were uncomplicated by mitral valve disease. In another study 39 per cent of cases with both mitral and aortic valve disease had also tricuspid stenosis of some degree (Einsel Feil and Stone 1931). A later analysis by Cooke and White (1941) has shown affection of the tricuspid valve in 47 (22 per cent) of 217 cases of rheumatic heart disease among 4 300 autopsies at the Massachusetts General Hospital between 1920 and 1937 but in only 30 of these (14 per cent) was tricuspid stenosis thought to be of sufficient degree to be of clinical importance. Another study by Smith and Levine (1942) revealed 32 cases of tricuspid stenosis among 340 individuals with rheumatic valvular disease in 4 437 autopsies at the Peter Bent Brigham Hospital from 1913 to 1940 inclusive.

**Etiology.** The causes of tricuspid valve disease are exactly those of mitral disease most commonly the rheumatic type of infection with verrucose endocarditis thickening of the valve on healing with fusion of cusps and fusion and shortening of the chordae tendineae in advanced cases. Acute and sub-acute bacterial endocarditis sclerosis and trauma are rare causes of tricuspid disease as are also such congenital defects as displacement and insufficiency (Ebstein 1866 Yater and Shapiro 1937) stenosis and atresia.

The age and sex incidences of tricuspid valve disease correspond roughly to those of mitral disease children and young adults chiefly being affected and females slightly more often than males although in one series of cases the sexes were evenly divided (21 to 21) and the age at death averaged very much less than that in rheumatic heart disease in general (23 years as compared with 42 years) (Cooke and White 1941).

**Pathology.** Pathologically in tricuspid valve disease as in the case of the mitral valve regurgitation and stenosis are almost invariably associated although either one may preponderate. Stenosis of clinical importance and in some cases diagnosable clinically is reached when the circumference of the adult tricuspid valve ostium normally 11 to 13 cm (average 12 cm) is reduced

to 8 cm or less. The appearance of the stenosed tricuspid valve is much like that of the stenosed mitral valve in fact when there is a tricuspid diaphragm with a small ostium in its center a view from above looking into both atria gives a strikingly symmetrical appearance on both sides. Functional tricuspid regurgitation is common with right ventricular dilatation associated with congestive heart failure (Figure 126 page 671) but occurs also with other factors like anemia and pulmonary regurgitation.

*Effect of tricuspid valve disease on the heart.* Well marked tricuspid stenosis if uncomplicated naturally affects little of the heart itself except the right atrium which becomes enlarged. Tricuspid regurgitation causes enlargement of both right heart chambers. Since however there is practically always involvement of some other valve as well as of the tricuspid one finds a combination of effects on the heart chambers. Practically speaking tricuspid stenosis acts wholly on the circulation as a process obstructing the return of blood to the heart comparable to the effect of chronic constrictive pericarditis and is not a factor causing myocardial strain or failure except in very rare congenital cases.

*Symptoms and signs.* Tricuspid valve disease usually causes neither symptoms nor distinctive clinical signs. If it is considerable there may be suggestive signs and rarely conclusive evidence if not masked by complicating factors like mitral disease and heart failure.

*Tricuspid stenosis* of high degree may give rise to a muddiastolic murmur heard maximally at the lower end of the sternum but usually distinguishable with difficulty if at all from the more marked mitral stenosis murmur transmitted from the apex. In very rare cases the two different murmurs may be sharply localized or the tricuspid murmur may be preponderant. Other corroborative signs of tricuspid stenosis are right atrial enlargement (see Figure 120 page 651) increased jugular venous pulse (*especially a marked chronic deep systolic jugular pulse* in the absence of an irreversible tricuspid ring dilatation) liver pulsation in the absence of other evidence of congestive failure and fluoroscopically enlargement and pulsation of the superior vena cava and unusually clear lung fields with a tendency of the esophagus to be deviated to the left by the enlarged right atrium (superimposed on the big left atrium which in marked mitral stenosis more often displaces the esophagus to the right). The increased systolic pulsation of neck veins, vena cava and liver is of course due to tricuspid regurgitation but in the absence of pure dilatation of the tricuspid ring this means tricuspid valve deformity more often in the form of a diaphragm causing both stenosis and regurgitation. Almost invariably atrial fibrillation is present so that the jugular and liver pulses show only ventricular waves but in very rare cases normal rhythm persists and a very large *a* wave due to the contraction of the powerful and obstructed right atrium is seen in the neck veins as a striking phenomenon (Puddey 1951).

*Tricuspid regurgitation* due to valvular disease is more likely than is functional regurgitation due to heart failure to show a systolic murmur localized at the lower end of the sternum because in the former case the strength of



the ventricular contraction is greater and the tricuspid ostium does not tend to remain so wide open during systole. In the rare cases of well marked tricuspid regurgitation without heart failure the jugular and other venous pulses are especially pronounced with greatly exaggerated *c* or ventricular contraction waves without the sustained stasis waves uniting the *m* and *v* waves (see Chapter 8). It is important not to confuse the deep systolic jugular pulse with vigorous carotid arterial pulsation, an error frequently made. Fluoroscopically the superior vena cava and the right atrium are seen to pulsate markedly especially at the time of ventricular systole. Finally, the liver pulse is likely to be more marked than with any other conditions. It shows a great preponderance of the ventricular wave. Pulsation of the spleen also has been noted (Sutton and Rawson 1935). But there may be neither hepatic nor splenic pulsation evident clinically in proved cases of tricuspid stenosis. Other studies such as arterial blood pressure measurement and electrocardiography are of little or no value in the diagnosis of tricuspid valve disease; the electrocardiogram almost invariably shows right ventricular preponderance due to the mitral stenosis also present.

The course and prognosis, complications, and treatment of tricuspid valve disease are somewhat similar to those already noted in the discussion of mitral valve disease and in fact are almost invariably dependent on them, since the mitral lesion is usually greater in degree and far more important. There are however two qualifications necessary. In the first place the presence of tricuspid valve disease of importance signifies a higher degree of heart disease than when mitral or mitral and aortic valve disease is present without tricuspid valve deformity, and so death comes considerably earlier (averaging in Cooke and White's series only 23 years in contrast to 42 years for all the rheumatic heart cases) and in the second place after systemic venous congestion has set in life lasts longer in the cases with tricuspid stenosis than in those without, due to the protection of the heart and lungs by the mechanical obstruction of the stenosed valve from engorgement with blood. Thus well marked tricuspid stenosis acts much as does chronic constrictive pericarditis in causing an invalid or semi invalid life for years with little dyspnea but with big liver and ascites, often requiring paracentesis or diuretics, in contrast to the much shorter life of the patient with pure mitral stenosis after congestive failure has once set in. However there is no advantage at all in this for not only does the tricuspid patient have a longer spell of congestion but he lives a considerably shorter life than does the mitral case. The younger tricuspid patients who die succumb as a rule as do the younger mitral ones to the myocardial effects of recurrent active rheumatism. Surgical repair of deformed tricuspid valves has not yet been attempted so far as I am aware.

The differential diagnosis of tricuspid valve disease is very difficult and has been referred to above; stenosis of this valve may be indistinguishable from mitral stenosis while organic tricuspid regurgitation may give signs that easily lead to an incorrect diagnosis of mitral regurgitation with functional tricuspid regurgitation caused by right ventricular dilatation. The rare irreversible dilata-

tion of the tricuspid ring with little or no myocardial failure and without any tricuspid valve deformity (Fischer 1933) may be indistinguishable from tricuspid valve disease. Chronic constrictive pericarditis can be easily distinguished by the absence of any evidence of organic valvular disease in that condition.

## D PULMONARY VALVE DISEASE

Congenital stenosis of the pulmonic valve or of the right ventricular outflow tract (infundibulum) below it is one of the most important and interesting of all valvular defects. Although uncommon it has lately held the limelight. Other pulmonary valve lesions, congenital or acquired, are very rare. The other valves are usually normal when the pulmonary valve is deformed.

**Etiology.** The causes of pulmonary valve disease are as follows: first, congenital stenosis or atresia, the former (stenosis) with or without septal defect, the latter (atresia) always with such defect; second, rheumatic infection, which though it may attack the pulmonary valve acutely, very rarely leaves any deformity; third, acute and subacute bacterial endocarditis.

When pulmonary regurgitation is found, it is almost always functional in character and due to greatly increased pulmonary arterial blood pressure and pulmonary artery dilatation, resulting most commonly from advanced mitral stenosis.

**Pathology.** The usual pulmonary valve lesion of congenital nature consists of a fusion of the cusps generally into a diaphragm with a small opening in the middle of it, a high degree of stenosis resulting. In some cases this lesion appears to be the result of a fetal endocarditis. Normally the circumference of the adult pulmonary valve should measure 8 to 9 cm; it should be considered too small if it measures 6 cm or less. Rarely the cusps may be defective or absent so that regurgitation results. In some instances the base of the valve is a part of a narrow canal caused by faulty fetal development. The pulmonary artery itself may be smaller or larger than normal, or it may be of normal caliber, generally it is considerably enlarged when there is pulmonary valve stenosis.

In many of the cases of so-called congenital pulmonary stenosis the pulmonary valve itself is normal or simply of small size without other deformity, the stenotic lesion being located in the region of the infundibulum of the right ventricle 2 or 3 cm below the valve and often separated from it by a cavity of variable size. This should actually be called infundibular stenosis. In such cases there is usually an interventricular septal defect and often dextroposition of the aorta, giving rise (with right ventricular hypertrophy) to the commonest adult lesion associated with the morbus caeruleus or *maladie bleue*, namely the tetralogy of Fallot (see Chapter 13).

An abnormal number of cusps, two or four, sometimes comes from fetal maldevelopment, and a very rare congenital defect is valvular deficiency with regurgitation resulting.

Acquired organic pulmonary regurgitation is rare and usually due to bacterial endocarditis complicating congenital heart disease pathologically it resembles bacterial endocarditis of the aortic valve

Aschoff bodies have been found in the pulmonary valve in active rheumatic heart disease but it is rare for the rheumatic infection to result in any actual deformity of the pulmonary valve

*The effect of pulmonary valve lesions on the heart* The effect of pulmonary valve lesions is primarily on the right ventricle causing hypertrophy and in the case of regurgitation and of failure dilatation also The largest right ventricle is found with congenital pulmonary stenosis its weight often exceeding that of the left ventricle and even reaching a figure three times the normal in such a case the cardiac apex is made up more by the right ventricle than by the left (Figure 64 page 299) The myocardium strongly hypertrophied is usually healthy but it may eventually fail under the strain of the valvular defect The right atrium also is as a rule enlarged with pulmonary valve disease

*The effect of pulmonary valve lesions on the pulmonary artery* Infundibular stenosis of congenital origin generally a part of the tetralogy of Fallot is accompanied by a pulmonary artery and circulation of smaller caliber than normal unless there are other congenital defects giving rise to dilatation of the artery On the other hand pulmonary valve stenosis and pulmonary regurgitation are attended by some dilatation of the artery most marked of course in the functional cases when the arterial dilatation precedes the valvular deficiency

*Symptoms and signs* There are no symptoms of pulmonary valve disease apart from those of associated conditions such as congenitally defective circulation, bacterial endocarditis, and heart failure There are a few characteristic signs

*Pulmonary stenosis* gives a harsh systolic murmur accompanied by a palpable thrill maximal in the second intercostal space just to the left of the sternum this murmur with thrill is diagnostic if aortic stenosis patent ductus arteriosus interventricular septal defect and aortic aneurysm can be excluded such exclusion is usually an easy procedure Cardiac enlargement is not marked when it involves the right ventricle but physical examination and roentgen ray study often show an increase of dullness and shadow transversely to the left sometimes giving the characteristic coeur en sabot shape of marked right ventricular preponderance with decreased pulmonary vascular shadows The electrocardiogram shows the highest degree of right ventricular preponderance found in any condition with abnormally large P waves due to the right atrial enlargement (Figure 73 page 320) If a congenital ventricular or atrial septal defect is also present there is cyanosis often of high degree as in the tetralogy of Fallot In the markedly cyanotic cases polycythemia and clubbing of the fingers are evident (see Chapter 13)

*Pulmonary regurgitation* whether due to structural valve defect or functionally produced by pulmonary hypertension and pulmonary artery dilatation gives a blowing early diastolic murmur along the left sternal border that can

not always be distinguished in site time and character from that due to aortic regurgitation it tends to begin higher up however and often follows immediately after a greatly accentuated pulmonary second sound The distinction between pulmonary regurgitation and aortic regurgitation must some times be made by other characteristics than the murmur itself but there may be no clues in the case of very slight lesions except when the defect is functional the big pulmonary artery and perhaps also marked mitral stenosis being evident When the pulmonary regurgitation is pronounced a visible pulsation is evident in the second left interspace and vigorous pulsation of pulmonary artery right ventricle and pulmonary hilus shadows is seen fluoroscopically The pulmonary second sound is usually increased with regurgitation if the valve cusps are not badly damaged and it is decreased or absent with stenosis

**Course and prognosis** The course and prognosis of pulmonary valve lesions depend on the extent of the lesions With considerable congenital stenosis and much cyanosis life is usually short although there are rare instances on record of patients surviving to middle life or to early old age having lived useful active lives The lesser grades of stenosis without cyanosis are less serious I have followed for many years a frail woman cyanotic since early childhood with clubbed fingers and all the signs of pulmonary valve stenosis who finally died in the year 1949 of right heart failure at the age of 75 years She showed at postmortem examination marked pulmonary valve stenosis and an atrial septal defect She survived 18 years longer than the oldest case with these defects previously recorded Although the very rare cases of pulmonary regurgitation due to valvular disease are under considerable strain they may support moderately active lives for years Patients with functional pulmonary regurgitation do badly usually living but a few months or a year or two at best the valve not being itself responsible for the bad prognosis as it is merely a part of the terminal stage of marked mitral stenosis or pulmonary heart disease Death that may ensue in some cases of subacute or acute bacterial endocarditis is due not to the pulmonary valve involvement if present but to the active infection itself

**Complications** The chief complications of pulmonary valve disease are right ventricular failure and subacute bacterial endocarditis Disease of other heart valves may infrequently be associated with important lesions of the pulmonary valve rarely all four valves are involved in rheumatic heart disease

**Treatment** In the last edition of this book (1944) I stated that there was no special treatment for pulmonary valve disease surgical or medical but that the victim should be protected from overexertion and infection the underlying disease treated if possible and complications cared for During the years that have intervened however two surgical procedures have been introduced in treatment the first consisting of arterial anastomosis between the aorta or its branches and a pulmonary artery to bring blood to the lungs to be oxygenated thus by passing the stenosed pulmonary valve ostium in cases of the morbus caeruleus in particular the tetralogy of Fallot (Blalock and Taussig 1945

Potts 1946) and the second consisting of cutting the stenosed valve itself (Brock 1948) (see Chapter 13 for details)

### E COMBINED VALVULAR DISEASE

There is no need of any particular discussion about disease of two or more valves in the same case. The etiology, pathology, signs, and treatment are as outlined for the individual valve lesions. The course and prognosis are naturally more serious the more valves there are involved, provided the degree of damage to the individual valves is comparable; there is no exception in the case of well marked tricuspid stenosis which at one time was thought to improve the prognosis of other valve lesions with which it is associated. Before carefully collected data corrected the error which had arisen from comparison of the duration of 'congestive failure' in the cases with and without tricuspid stenosis (see above under Tricuspid Valve Disease). The commonest valve disease combinations are mitral plus aortic and mitral plus tricuspid (see Chapter 24). In about three quarters of all cases with combined valvular disease the mitral lesion is the essential and controlling one, and in the other quarter the aortic valve defect requires the chief consideration.

### F INTRACARDIAC THROMBOSIS

Intracardiac thrombosis is a common complication of many cardiac conditions: stasis, old scarring of the endocardium, infection, and infarction. It was found post mortem in 265 or 34.4 per cent of 771 consecutive adult autopsied patients who died of heart disease (Garvin 1941). It is almost always bland, but as in bacterial endocarditis may become infected itself. It is nearly always attached to the wall of one of the heart chambers, loosely or tightly, constituting a *mural thrombus* in left ventricle, left atrium, right atrium, or right ventricle, or in more than one chamber. *Free or ball thrombi* are rare, being found in a few cases of mitral stenosis in the left atrium where they may mechanically seriously obstruct the circulation, even causing attacks of syncope and marked feebleness of the pulse with acrocyanosis, and in extreme cases purpura and gangrene of the extremities, toes, fingers, and ears. Pedunculated thrombi in the left atrium may act much like ball thrombi. A unique case of a ball thrombus in the right atrium has also been reported; it was correctly diagnosed ante mortem (Wright et al. 1944).

The commonest cause of mural thrombi in the heart is myocardial infarction, fresh or old, involving almost always the left ventricle and responsible for occasional peripheral arterial embolism to eye, brain, kidney, mesentery, arm, or leg. Rheumatic heart disease ranks second, with thrombosis on the wall of the left atrium or in its appendage, especially in the presence of atrial fibrillation which so commonly complicates mitral stenosis. Bacterial endocarditis, subacute or acute, is next most common as a cause of important intracardiac thrombosis, in such cases located chiefly on the valves. Large emboli may be ejected from the heart in either rheumatic heart disease or subacute bacterial

endocarditis Intracardiac thrombi may be found also in coronary heart disease without infarction hypertensive heart disease, and aortic valve disease syphilitic or rheumatic especially if the left ventricle and left atrium are dilated it is rare in congenital heart disease and in the cor pulmonale It is common for a mural thrombus to be laid down in successive layers in a cardiac as in an aortic aneurysm the deeper layers slowly undergoing organization and incorporation in the endocardium itself Anticoagulant therapy carried on for months or even years under close supervision may be very helpful in reducing the incidence of peripheral embolism from intracardiac thrombosis

## BIBLIOGRAPHY

### ENDOCARDIAL DISEASE VALVULAR LESIONS INTRACARDIAC THROMBOSIS

SEE ALSO REFERENCES UNDER GENERAL REFERENCES FOLLOWING CHAPTER 2 AND IN CHAPTERS 5 SOUNDS AND MURMURS 7 ROENTGENOLOGY 9 ELECTROCARDIOGRAPHY 13 CONGENITAL CARDIOVASCULAR DEFECTS 14 RHEUMATIC HEART DISEASE 15 ACUTE AND SUBACUTE BACTERIAL (INFECTIVE) ENDOCARDITIS AND 16 CARDIOVASCULAR SYPHILIS

#### General

- Anitschkow N "Atherosclerosis (Lipoidosis) of the Heart Valves and Its Relation to Endocarditis" *Libman Anniversary Volumes* 1932 I 65
- Cabot, R C *Facts on the Heart* W B Saunders Co Philadelphia 1926
- Clawson B J Bell E T and Hartzell T B "Valvular Diseases of the Heart with Special Reference to the Pathogenesis of Old Valvular Defects" *Am J Path* 1926 II 193
- Comeau W J "Diffuse Parietal Endocardial Sclerosis Review of the Literature and Report of Two Cases" *Am J Path* 1937 XIII 277
- Cowper W "Of Ossifications or Petrifications in the Coats of Arteries Particularly in the Valves of the Great Artery" *Phil Tr Roy Soc London* 1706 XXIV 1970
- Davie T B "Tuberculous Verrucose Endocarditis" *J Path & Lact* 1936 XLIII 313
- Epstein H S "Comparative Study of Valvular Calcifications in Rheumatic and in Non-rheumatic Heart Disease" *Arch Int Med* 1940 LXV 279
- Grant H T "Observations on Endocarditis" *Guys Hosp Rep* 1936 LXXXVI 20
- Gross L "The Heart in Atypical Verrucose Endocarditis (Libman-Sacks)" *Libman Anniversary Volumes* 1932 II 527
- "The Significance of Blood Vessels in Human Heart Valves" *Am Heart J* 1937 XIII 275
- Hirschfelder A D *Diseases of the Heart and Aorta* J B Lippincott Co Philadelphia 3rd ed revised 1918 (1st ed 1910)
- Jones C H *Pathological and Clinical Observations Respecting Morbid Conditions of the Stomach* J Churchill London 1855 Case 17 (Functional aortic insufficiency in anemia)
- Kaufmann R "Über autoptische Befunde bei Herzkrankheiten" *Med Klinik* 1927 XXIII 1919
- Libman E., and Sacks B "A Hitherto Undescribed Form of Valvular and Mural Endocarditis" *Arch Int Med* 1924 XXXIII 701
- Sperling F *Ueber Embolien bei Endocarditis* Inaugural dissertation Berlin 1872.
- White E D and Jones T D "Heart Disease and Disorders in New England" *Am Heart J* 1918 III 30

#### Recent References (1944-1950)

- Ashworth C T "Atherosclerotic Valvular Disease of Heart" *Arch Path* 1946 XLII 85

- Baron E. and Ritter D. W. "Endocardial Tuberculosis" *Ann Int Med* 1950 XXXIII, 1023
- Collier F. C. and Rosahn P. D. "Endocardial Fibroelastosis: Report of Two Cases" *Pediatrics* 1951 VII 175
- Cosgrove G. E. Jr. and Kaump D. H. "Endocardial Sclerosis in Infants and Children" *Am J Clin Path* 1946 XVI 322
- Davies J. N. P. "Endocardial Fibrosis in Africans" *East African M J* 1948 XXV 10
- Gardner F. E., and White P. D. "Coronary Occlusion and Myocardial Infarction Associated with Chronic Rheumatic Heart Disease" *Ann Int Med* 1949 XXXI 1003
- Neuenschwander H. L., Miller J. R. and Briggs J. F. "A Survey of Valvular Heart Disease in 1 000 Cases of Pulmonary Tuberculosis" *Minnesota Med* 1949 XXVII 378
- Neumann Prof. "Ochronosis of Heart Valves: Personal observations in Pathological Institute in Brno Moravia" August 1946
- Mitral Valve Disease** (See also references under Cardiac Enlargement in Chapter "5 Abnormalities of Myocardium and of Heart Chambers and Surgery for Valvular Disease" later in the Bibliography of this chapter)
- Blackford L. M. "Mitral Stenosis as a Cause of Angina Pectoris" *Am Heart J* 1940 XX 492
- Bland E. F., Jones T. D. and White P. D. "Disappearance of the Physical Signs of Rheumatic Heart Disease" *JAMA* 1936 CVII 569
- Bland E. F., White P. D. and Jones T. D. "The Development of Mitral Stenosis in Young People with a Discussion of the Frequent Misinterpretation of a Midsystolic Murmur at the Cardiac Apex" *Am Heart J* 1935 X 995
- Cabot R. C. "Mitral Stenosis: Observations on 200 Cases Before and After Death. Also on 116 Not Autopsied" *Tr A Am Physicians* 1914 XXIX 22
- Cossio P. "Choque de la punta mitral" *Rev Argentina de Cardiol* 1943 X 149
- Dressler W. "Mitral Stenosis and Angina Pectoris" *Clinical Cardiology* Paul B. Hoeber Inc. New York 1942 page 200
- Einsel I. H., Feil H. S. and Stone C. S. "Clinical and Pathological Study of Seventy Cases of Mitral Stenosis" *Ohio State M J* 1931 XXVII 783
- Harris A. W. and Levine S. A. "Cerebral Embolism in Mitral Stenosis" *Ann Int Med* 1941 XV 637
- Hellwig C. A. "Atheromatosis of the Mitral Valve" *Am Heart J* 1943 XXIV 41
- Keliber E. E. "Long Standing Productive Cough as the Chief Clinical Manifestation in Mitral Stenosis" *Ann Int Med* 1941 XV 899
- Levine H. H. and White P. D. "Pulmonary Infarction Complicating Severe Disease of Mitral Valve" *Arch Int Med* 1937 LX 39
- Levine S. A. and Kauvar A. J. "The Association of Angina Pectoris or Coronary Thrombosis with Mitral Stenosis" *J Mt Sinai Hosp* 1942 VIII 754
- McGinn S. and White P. D. "Acute Pulmonary Congestion and Cardiac Asthma in Patients with Mitral Stenosis" *Am Heart J* 1934 IX 697
- Marks J. H. "Calcification in the Annulus Fibrosus of the Mitral Valve" *New England J Med* 1936 CCXIV 411
- Parker F. Jr. and Weiss S. "Nature and Significance of Structural Changes in Lungs in Mitral Stenosis" *Am J Path* 1936 XII 573
- Samojloff A. and Steshinsky M. "Ueber die Vorhoferhebung des Elektrokardiogramms bei Mitralstenose" *Munch med Wchnschr* 1909 LVI 1942
- Samways H. W. "The Left Auricle in Mitral Stenosis: Hypertrophy and Dilatation." *Brit M J* 1896 II 1567
- Sutton D. C. and Rawson V. "A Case of Pulsating Spleen in Mitral and Tricuspid Disease" *Am Heart J* 1935 X, 1096
- Vicussens E. *Traité nouveau de la structure et des causes du mouvement naturel du coeur* Jean Guillemette Toulouse 1715
- White P. D. and Bland, E. F. "Mitral Stenosis After Eighty with Especial Reference to Dr Herman F. Vickery" *JAMA* 1941 CXVI 2001
- Williams C. J. B. *Diseases of the Chest* John Churchill Publisher London 3rd ed 1834 page 198

## Recent References (1944-1950)

- Aarseth, S "Hemosiderosis of Lungs in Mitral Stenosis" *Nord med* 1948 XL, 2216
- Bailey O T and Hickam J B "Rupture of Mitral Chordae Tendineae" *Am Heart J* 1944 XXVIII 578
- Bourne G "Embolism in Mitral Stenosis" *Brit Heart J* 1950 XII 263
- Bu taman e Riofrio H Kohout F and Schlesinger P "Considerações estatístico-clínicas sobre 110 casos de estenose mitral" *Arq brasil de cardiol* 1951 IV 1
- Ceballos Labat J and Logsdon Ch "Estudio radiológico de las siluetas producidas por la doble lesión mitral y la estenosis mitral pura" *Arch del Inst de cardiol de Mexico* 1950 XX, 338
- Chapman D W Huggins R A and Glass W G "Measurement of Blood Flow and Effects of Cardiodynamics with a Venous Shunt in Mitral Stenosis" *J Clin Investigation* 1950 XXIX 803
- Gorlin R Dexter L and Harken D E "Circulatory Changes in Mitral Stenosis Following Valvuloplasty" *J Clin Investigation* 1951 XXX 643
- Gorlin, R., and Gorlin S G "Hydraulic Formula for Calculation of the Area of the Stenotic Mitral Valve Other Cardiac Valves and Central Circulatory Shunts" *Am Heart J* 1951 XLI 1
- Gorlin, R., and Haynes F W "Physiologic Method for Calculation of Cross Sectional Area of the Mitral Valve" *J Clin Investigation* 1950 XXIX 817
- Gumpert T E "Miliary Appearances in Lungs in Mitral Stenosis Endogenous Pulmonary Hemosiderosis" *Brit M J* 1947 II 488
- Holovsky M "The Symptomatology and Differential Diagnosis of Mitral Stenosis Without Valvular Lesions" *Ann med Vienna* 1947 II 540
- Hurst A Bassin S and Levine I "Miliary Densities Associated with Mitral Stenosis" *Am Rev Tuberc* 1944 XLIX 276
- Jordan R A Scheffley C H and Edwards J E "Mitral Thrombosis and Arterial Embolism in Mitral Stenosis A Clinicopathologic Study of Fifty-one Cases" *Circulation* 1951 III 363
- Laubry C Lenegre J and Abbas L "Les ombres radiologiques pulmonaires du type micronodulaires chez les cardiaques L'hemosiderose pulmonaire" *Acta Cardi* 1948 III 91
- Lewis, B M et al. "The Relation of Mitral Valve Area to Clinical Status in Patients with Mitral Stenosis" *J Clin Investigation* 1951 XXX 656
- Pendergrass E P Lane E L and Ostrum H W "Hemosiderosis of the Lung Due to Mitral Disease A Report of Six Cases Simulating Pneumoconiosis" *Am J Roentgenol* 1949 LXI 443
- Rasmussen H and Nyhus O "The Electrocardiogram in Mitral Stenosis with Special Regard to Its Development A Study of 100 Cases" *Acta med Scandinav* 1948 CXXIX 446
- Sokoloff L Elster S A and Righthand N "Sclerosis of the Chordae Tendineae of the Mitral Valve" *Circulation* 1950 I 783

## Aortic Valve Disease

- Bonet T *Sepulchretum sive Anatomia Practica* Leonard Chouet, Geneva 1679 Vol I Book II Section VI (De morte repentina, on sudden death) Observation XXVI
- Chevers N "Observations on the Diseases of the Orifice and Valves of the Aorta" *Guy's Hosp Rep* 1842 VII, 387
- Cortigan, D J "On Permanent Patency of the Mouth of the Aorta or Inadequacy of the Aortic Valves" *Edinb med M & S J* 1832 XXXVII 225
- Durozier, P "Du double souffle intermittent crural comme signe de l'insuffisance aortique" *Arch gén de méd Paris* 1861 I 417 588
- Garvin C F "Functional Aortic Insufficiency" *Ann Int Med.* 1940 XIII 1799
- Karner H T., and Koletska S "Calcific Sclerosis of the Aortic Valves" *Tr A Am Physicians* 1940 LV 188
- Calcific Disease of the Aortic Valve J B Lippincott Co Philadelphia, 1947
- McGinn S and White P D "Clinical Observations on Aortic Stenosis" *Am J M Sc* 1934 CLXXXVIII 1



- Marvin H M, and Sullivan A G Clinical Observations upon Syncope and Sudden Death in Relation to Aortic Stenosis *Am Heart J* 1935 X 705
- Monckeberg J G "Der normale histologische Bau und die Sklerose der Aortenklappen." *Virch Arch f path Anat* 1904 CLXXVI 472

*Recent References (1944-1950)*

- Fenichel N M Arteriosclerotic Aortic Insufficiency *Am Heart J* 1950 XL 117
- Gruenwald P Subaortic Stenosis of the Left Ventricle *Bull Internat A M Museums* 1947 XXVII 173
- Hammarsten J P Syncope in Aortic Stenosis *Arch Int Med* 1951 LXXXVII 74
- Horan M J Jr and Barnes A R Calcarenous Aortic Stenosis and Coronary Artery Disease *Am J M Sc* 1948 CCXV 451
- Rasmussen H "The Electrocardiogram in Aortic Insufficiency with Special Regard to the Development of the Left Bundle Branch Block Electrocardiogram" *Acta med scand* 1944 CXVIII 385
- Wilens E L Pierce J M and Fallas Diaz M La incidencia relativa de la enfermedad valvular reumática en Costa Rica y Nueva York y sus relaciones con el origen reumático de la estenosis calcáreo aortica *Revista med de Costa Rica* 1945 XII 479

*Diseases of Other Valves (See also references in Chapter 13 Congenital Heart Disease)*

- Altschule M D and Blumgart H L The Circulatory Dynamics in Tricuspid Stenosis Their Significance in the Pathogenesis of Edema and Orthopnea *Am Heart J* 1937 XIII 589
- Cooke W T and White P D Tricuspid Stenosis with Particular Reference to Diagnosis and Prognosis *Brit Heart J* 1941 III 147
- Dressler W and Fischer R Ueber Trikuspidalstenose Ein Bericht über 30 autopsisch sichergestellte Fälle *Alin Wehnschr* 1929 VIII 1267 and 1316
- Ebstein W Ueber einen sehr seltenen Fall von Insufficienz der Valvula tricuspidalis, bedingt durch eine angeborene hochgradige Missbildung derselben" *Arch f Anat u Physiol* 1866 III 238
- Fischer R "Epikrise eines Falles von Trikuspidalinsuffizienz." *Wien klin Wchnschr* 1933 XLVI 1544
- Hardin B L Jr and Daniels W B Tricuspid Stenosis Report of a Case with Involvement of All Four Valves of the Heart *Ann Int Med* 1942 XVII 536
- Holzmann M "Röntgenbefunde bei Trikuspidalfehlern" *Fortschr a d Geb d Röntgenstrahlen* 1932 XLVI 14
- King T W The Safety Valve Function in the Right Ventricle of the Human Heart *Guys Hosp Rep* 1837 II 132
- Leudet R Rétrécissement tricuspidien Paris Thesis 1888
- Osler W and Gibson A G Diseases of the Valves of the Heart Chapter VIII of Vol IV *Modern Medicine* edited by Osler and McCrae Lea & Febiger Philadelphia 2nd ed 1915
- Smith J A and Levine S A "The Clinical Features of Tricuspid Stenosis" *Am Heart J* 1942 XXIII 739
- Tschilikin W I "Zur klinischen Charakteristik der Trikuspidalstenose" *Ztschr f Kreislauff* 1930 XXII 177
- Winsor T and Burch G E "Study of Incidence of Tricuspid Regurgitation at Large General Hospital in the South" *South M J* 1942 XXXV 1065
- Yater W M and Shapiro M J Congenital Displacement of the Tricuspid Valve (Ebstein's Disease) Review and Report of a Case with Electrocardiographic Abnormalities and Detailed Histologic Study of the Conduction System" *Ann Int Med* 1937 XI 1043

*Recent References (1944-1950)*

- Acceves S and Carral E "Diagnóstico de las lesiones tricuspidales" *Arch del Inst de Cardiol de Mexico* 1947 XVII 701
- Denolin H Lequime J Goksel F and Pannier III La tresse tricuspidienne Étude clinique et physiopathologique de deux cas *Acta cardiol* 1950 V 400

- Martin W B and Spink W W "Endocarditis Due to Type B Hemophilus Influenzae Involving Only the Tricuspid Valve" *Am J M Sc* 1947 CCXIV 139
- Messer A L, Hurst J W, Rappaport M B and Sprague H B "A Study of the Venous Pulse in Tricuspid Valve Disease" *Circulation* 1950 I 388
- Puddu V "An Unusual Aspect of the Venous Pulse Probably Due to Tricuspid Stenosis Dynamically Pure Without Failure" *Am Heart J* 1951 in press
- Rogers H M, Domeier L H, Brigham F G and White P D "Tricuspid Stenosis with Survival to the Age of 61 Years" *Am Heart J* 1950 XXXIX 761
- Taquini A C "Cardiac Failure in Tricuspid Disease" *Am Heart J* 1947 XXXIII 727
- White P D, Hurst J W and Fennell R H "Survival to the Age of Seven and a Half Years with Congenital Pulmonary Stenosis and Patent Foramen Ovale" *Circulation* 1950 II 558

### Surgery for Valvular Disease

- Allen D S and Graham E A "Intracardiac Surgery—A New Method Preliminary Report" *JAMA* 1922 LXXIX 1078
- Cutler E C and Beck C S "The Present Status of the Surgical Procedures in Chronic Valvular Disease of the Heart" *Arch Surg* 1929 XVIII 403
- Tuffer T and Carrel A "Patching and Section of the Pulmonary Orifice of the Heart." *J Exper Med* 1914 XX 3

### Recent References (1944-1950)

- Bailey C P "Surgical Treatment of Mitral Stenosis (Mitral Commissurotomy)" *Dis of Chest* 1949 XV 377
- Bailey C P, Glover R P and O'Neill T J E "Surgery of Mitral Stenosis" *J Thoracic Surg* 1950 XIX, 16
- Bailey C P, Glover R P, O'Neill T J E and Redondo Ramirez, H P "Experiences with the Experimental Surgical Relief of Aortic Stenosis. A Preliminary Report" *J Thoracic Surg* 1950 XX 516
- Bailey C P, O'Neill T J E, Glover R P, Jamison W L and Redondo Ramirez, H P "Surgical Repair of Mitral Insufficiency (A Preliminary Report)" *Dis of Chest* 1951 XIX, 175
- Baker C, Brock R C and Campbell M "Valvulotomy for Mitral Stenosis. Report of 6 Successful Cases" *Brit M J* 1950 I 1283
- Bill A H Jr, Pearce E C II and Gross R E "Experimental Production of Extra-cardiac Shunt Around Mitral Valve. Preliminary Report" *Arch Surg* 1950 LXX 3114
- Blalock A and Taussig H B "Surgical Treatment of Malformations of the Heart" *JAMA* 1945 CXXV 189
- Bland E F and Sweet R H "A Venous Shunt for Marked Mitral Stenosis" *A* 1949 CXL 1259
- Brock R C "Pulmonary Valvulotomy for Congenital Pulmonary Stenosis" *J* 1948 I 1121
- Brock R C and Campbell M "Valvulotomy for Pulmonary Valvular Stenosis" *Heart J* 1950 XII 377
- "Infundibular Resection or Dilatation for Infundibular Stenosis" *Dis of Chest* 1950 I 403
- Burdette W J "Removal of the Auricular Appendage and Its Possible Therapeutic Value. A Preliminary Report" *New Orleans M & S J* 1948 CI 228
- Dallaines F, Lenègre J, Dubost C, Mathivat A and Sebah, L. "Ligation of the pulmonary vein azygos dans le rétrécissement mitral à propos d'un cas opéré avec succès" *Arch d mal d coeur* 1949 XLII 456
- Glover R P, Bailey C P and O'Neill T J E "Surgery of Stenotic Valvular Disease of the Heart" *JAMA* 1950 CXLIV 1049
- Glover R P, O'Neill T J E and Bailey C P "Commissurotomy for Mitral Stenosis" *Circulation* 1950 I 329
- Harken D E, Ellis L H and Norman L R "Surgical Treatment of Mitral Stenosis. II. Progress in Developing Controlled Valvuloplastic Technique" *J Thoracic Surg* 1950 XIX, 1

- Harken D E Ellis L B Ware P F and Norman L E "Surgical Treatment of Mitral Stenosis I Valvuloplasty *New England J Med* 1948 CCXXXIX, 801
- Murray G Cardioscope *Angiology* 1950 I 334
- Perianes I and Berreta J A Artificial Aortic Valve Experiments in Animals. *Medicina* 1949 IX 29
- Potts W J Smith S and Gibson S: Anastomosis of Aorta to Pulmonary Artery *JAMA* 1946 CXXXII 627
- Smithy H G Boone J A and Stallworth J M Surgical Treatment of Constrictive Valvular Disease of the Heart *Surg Gynec & Obst* 1950 XC 175
- Smithy H G Pratt Thomas H R and Deyerle H P Aortic Valvulotomy Experimental Methods and Early Results *Surg Gynec & Obst* 1948 LXXXVI 413
- Thompson S A Conversion of the Auricular Appendage into a Leakproof Valve Tube for Intracardiac Surgery *JAMA* 1950 CXLIV 1057

### Intracardiac Thrombosis

- Baronofsky I D and Skinner A Ligation of Left Auricular Appendage for Recurrent Embolization *Surgery* 1950 XXVII 848
- Cosgriff E W "Prophylaxis of Recurrent Embolism of Intracardiac Origin. Prolonged Anticoagulant Therapy on an Ambulatory Basis *JAMA* 1950 CXLIII 870
- Evans M E Ball Thrombus of the Heart *Brit Heart J* 1948 X 34
- Evans W and Benson R Mass Thrombus of the Left Auricle *Brit Heart J* 1948 X 39
- Garvin C F Ball Thrombi in the Heart *Am Heart J* 1941 XXI 371
- Mural Thrombi in the Heart *Am Heart J* 1941 XXI 713
- Kaplan D and Hollingsworth E W Pedunculated Thrombus of the Left Auricle Simulating Mitral Stenosis *JAMA* 1935 CV 1264
- Madden J L Resection of the Left Auricular Appendix A Prophylaxis for Recurrent Arterial Emboli *JAMA* 1949 CXL 769
- Schwartz S P and Biloon S The Clinical Signs of Occluding Thrombi of the Left Auricle *Am Heart J* 1931 VII 84
- Soderstrom N Myocardial Infarction and Mural Thrombosis in the Atria of the Heart. *Acta med Scandinav* 1948 CXXXII Suppl 217
- Soulie P Chiche P and Papanicolas I "Les thromboses parietales organisees des cavites du coeur *Arch d mal d coeur* 1949 XLII 669
- Wright I S et al "Ball Thrombus in the Right Auricle of the Heart with a Description of the Symptoms Produced *Am Heart J* 1944 XXVII 858

---

## CHAPTER 27

---

### PERICARDIAL DISEASE ACUTE AND CHRONIC PERICARDITIS WITH AND WITHOUT CONSTRICTION

---

Pericardial disease which has been recognized longer than any other pathologic cardiac condition (its recognition dates back to the Middle Ages) has continued since the last edition of this book to be the subject of clinical investigations which have led to important advances in its diagnosis and treatment.

Disease of the pericardium is a common condition occurring less often as an isolated lesion than as a part of acute heart disease especially rheumatic carditis and cardiac infarction or as a part of a polyserositis (with pleuritis or peritonitis) or of a systemic disease like septicemia or carcinomatosis. It may be serious in itself or merely an incident in other serious often fatal diseases or it may be wholly unimportant. It is found in about 5 per cent of postmortem examinations and is present as an acute condition in one half to two thirds of these cases. A survey made of 8 912 necropsies at the Mayo Clinic (Smith and Willis 1932) showed pericarditis in 373 cases (4.2 per cent). 215 (58 per cent) of these 373 cases had acute pericardial disease 113 with effusion and 102 fibrinous without effusion the latter including 40 instances of terminal pericarditis. 158 (42 per cent) had chronic pericarditis among which 15 cases had simply small localized patches (milk spots or soldier's patches). A more recent survey of 13 353 consecutive autopsies done in the Los Angeles County Hospital during a period of seven years (1940 to 1946 inclusive) revealed 729 cases (5.4 per cent) of pericarditis. nonspecific idiopathic pericarditis was the most frequent type found with rheumatic pericarditis next tuberculous and pneumonic pericarditis were decreasing in frequency (Griffith and Wallace 1949).

Disease of the pericardium is best considered under three headings acute pericardial disease chronic pericarditis and congenital defects.

- Harken D F Ellis L B Ware P F and Norman L R "Surgical Treatment of Mitral Stenosis I Valvuloplasty *New England J Med* 1948 CCXXXIX 881
- Murray G "Cardioscope *Annals* 1950 I 334
- Pertanés I and Berreta J A "Artificial Aortic Valve Experiments in Animals *Medicina* 1949 IX 29
- Potts W J Smith III and Gibson S "Anastomosis of Aorta to Pulmonary Artery *JAMA* 1946 CXXIX 627
- Smithy H G Boone J A and Stallworth J M "Surgical Treatment of Congenital Valvular Disease of the Heart *Surg Gynec & Obst* 1950 XC 175
- Smithy H G Pratt Thomas H R and Deyerle H P "Aortic Valvulotomy Experimental Methods and Early Results *Surg Gynec & Obst* 1948 LXXXVI 13
- Thompson S A "Conversion of the Auricular Appendage into a Leakproof Valve Tube for Intracardiac Surgery *JAMA* 1950 CXLIV 1057

### Intracardiac Thrombosis

- Baronofsky I D and Skinner A "Ligation of Left Auricular Appendage for Recurrent Embolization *Surgery* 1950 XXVII 848
- Cosgriff III W "Prophylaxis of Recurrent Embolism of Intracardiac Origin Protracted Anticoagulant Therapy on an Ambulatory Basis" *JAMA* 1950 CXLIII 80
- Evans M E "Ball Thrombus of the Heart *Brit Heart J* 1948 X 34
- Evans W and Benson R "Mass Thrombus of the Left Auricle *Brit Heart J* 1948 X 39
- Garvin C F "Ball Thrombus in the Heart *Am Heart J* 1941 XXI 371
- "Mural Thrombus in the Heart *Am Heart J* 1941 XVI 713
- Kaplan D and Hollingsworth E W "Pedunculated Thrombus of the Left Auricle Simulating Mitral Stenosis *JAMA* 1935 CV 1264
- Madden J I "Resection of the Left Auricular Appendix A Prophylaxis for Recurrent Arterial Emboli *JAMA* 1949 CXL 769
- Schwartz S P and Biloon S "The Clinical Signs of Occluding Thrombus of the Left Auricle *Am Heart J* 1931 VII 84
- Soderstrom N "Myocardial Infarction and Mural Thromboses in the Atria of the Heart *Acta med Scandinav* 1948 CXXXII Suppl 217
- Soulie P Chiche P and Papanicolaou I "Les thromboses parietales organisees des cavités du coeur *Arch d mal d coeur* 1949 XLII 669
- Wright I S et al "Ball Thrombus in the Right Auricle of the Heart with a Description of the Symptoms Produced *Am Heart J* 1944 XXVII 858

The more virulent infections like pneumonia are likely to cause a purulent rather than a serous effusion

*Purulent pericarditis* in which a variable amount of pus is found in the pericardial sac ■ ■ complication of disease produced elsewhere in the body by pyogenic bacteria such as pneumococci staphylococci and streptococci It may be of hematogenous origin or it may be produced by direct extension from an empyema or a mediastinal abscess It is sometimes difficult to say whether such pericarditis is purulent or serofibrinous when the effusion is not frankly composed of pus but contains a suspension of cells which are largely polymorphonuclear leukocytes Of a series of 300 fatal cases of pneumonia in an army base hospital 24 per cent showed acute pericarditis mostly of purulent nature (Stone 1919) but this is now becoming rare due to specific therapy with penicillin and other curative agents

*Hemorrhagic pericarditis* in which the exudate ■ largely bloody may be caused either by infection such as tuberculosis or fulminating rheumatic fever or by malignant disease This should be distinguished from *hemopericardium* due to hemorrhage into the pericardium the result of rupture of aortic or heart wall or of coronary vessel caused by infarction aneurysm or trauma

A rare cause of acute pericardial involvement is *malignant disease* generally metastatic but sometimes penetrating the pericardium from adjacent new growth in the mediastinum Sarcoma and carcinoma are the commonest lesions of this sort (Figure 118 page 594) but many varieties of new growths have been found secondary invasion of the pericardium is much more common than a primary tumor (see Chapter 23)

Still more rare is *pneumopericardium* due to the entrance of air from a pneumothorax from esophageal or bronchial perforation or from faulty paracentesis Rarely air has been intentionally introduced into the pericardial sac in the treatment of tuberculous effusion

*Age* Acute pericardial disease may occur at any age in accordance with the etiologic factors it is in general most common in youth when important infections are most frequent The majority of cases occur between the ages of 10 and 40 with an average of about 25 years

*Sex* There is a male sex preponderance in acute pericardial diseases of nearly 3 to 1 the cause for this is not clear (Cabot 1926 Smith and Willis 1932)

*Pathology* *Acute fibrinous pericarditis* consists of infiltration of the pericardium with many mononuclear and polymorphonuclear cells and ■ more or less adherent layer of fibrin containing such cells covering a part or the whole ■ of the pericardium starting on either the visceral ■ the parietal surface but as a rule eventually involving opposite surfaces Pericarditis due to infarction ■ usually limited to the area of necrosis in contradistinction to the general involvement of the pericardium by infection The exudate may be composed of a thin or ■ thick layer sometimes it is very massive even a centimeter or more in thickness It tends especially when thick to have an irregular uneven surface with stringy shredded masses of fibrin projecting like fur or complexly

interwoven such irregular surfaces have been termed shaggy or bread and butter pericarditis (Figure 134). A certain amount of increase of fluid in the pericardial sac (which normally contains 25 to 50 cc) is commonly found with fibrinous pericarditis. When the inflammatory or irritative process undergoes resolution and repair there may be left only a slight thickening of the pericardium, local or general. But when the acute process is marked in degree or extent adhesions, partial or complete, between the visceral and parietal

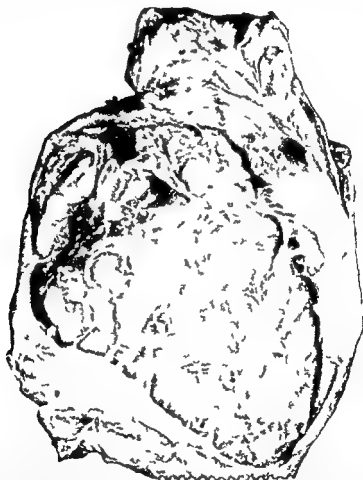


FIG. 134. Photograph of heart in a boy of 12 showing acute fibrinous pericarditis in case of advanced pyelonephritis of left kidney, congenital atresia of right kidney and uremia. (Kindness of Dr. Benjamin Castleman, Massachusetts General Hospital, Boston.)

pericardial surfaces are common and if the inflammatory reaction has been deep the heart may be firmly anchored to diaphragm, chest wall, pleura or mediastinum, or it may be encased in a firm, thick, unyielding, scarred, contracted pericardium with little or no serous sac left. Both of these pericardial abnormalities may coexist in the same case.

It is important to note that in practically all cases of pericarditis and particularly in those with severe involvement the subjacent myocardium is also affected it is doubtless this myocardial disease that is in the main if not wholly responsible for the electrocardiographic abnormalities in pericarditis

*Serofibrinous pericarditis* a type of pericardial effusion begins with fibrinous pericarditis but there is soon poured out in addition a serous exudate at varying speeds and of varying amounts from 100 up to 2 000 or 3 000 cc the latter only if the effusion is of slow development This extra fluid accumulates at first in the dependent parts of the sac but eventually it may distend the whole sac (Figures 135 and 136) unless it is withdrawn or subsides spontaneously If the amount is great there may develop extensive pressure on the surrounding structures—lungs mediastinal contents superior vena cava

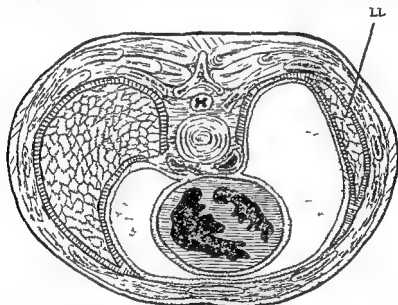


FIG 135 Diagram of cross section of thorax showing a very large pericardial effusion compressing the left lung (LL) (Conner *Am Heart J* 1926 I 431 Kindness of C V Mosby Company St Louis)

inferior vena cava and the mouths of the hepatic veins at the level of the diaphragm—along with dangerous pressure on the heart itself and on the great vessels within the pericardial sac (*cardiac tamponade*). Enormous effusions are sometimes seen usually tuberculous accumulating gradually and filling more than half the thoracic cavity In rare cases there may be a localized or pocketed pericardial effusion sometimes in unusual locations for example at the right upper border of the heart where it may simulate an aortic aneurysm such a limited effusion is the result of partial pericardial adhesions chronic or recent which prevent the effusion from taking the usual form

*Purulent pericarditis (pyopericardium)* If the exudate either on the surface of the pericardium or in the effusion fluid contains a great majority of poly



morphonuclear leukocytes it is called purulent, it may be thin (and watery) or thick (and creamy) and easy or difficult to aspirate

*Hemorrhagic pericarditis* simply signifies a high content of red blood corpuscles in the pericardial exudate sufficient to color it red, if the effusion is practically pure blood the term *hemopericardium* is employed

*Neoplasms* a rare cause of pericardial disease may or may not induce an effusion when such an effusion occurs it is usually bloody and may contain cancer cells



FIG 136 Roentgenograms in a case of subacute tuberculous pericarditis with effusion (A) Before paracentesis (B) after paracentesis air has been injected in the place of some of the fluid removed Note the thickened pericardium

**Symptoms** Acute pericardial disease is generally painless but there are two important conditions which give rise to symptoms (1) When the pleural or outer border of the diaphragmatic pericardium is involved frequently with complicating pleurisy pain results usually sharp intermittent or continuous much aggravated by or indeed sometimes felt only during inspiration and referred to precordium left shoulder and less often to the abdomen A large part of the pericardium especially the visceral surface can be inflamed without causing pain as is usually the case with the terminal dry or fibrinous pericarditis of uremia and with the pericardial involvement in cardiac infarction (2) The other important condition giving rise to symptoms in pericarditis is distention of the pericardium by a moderate or large effusion by air or by both air and fluid With small effusions there are no symptoms with large effusions especially those developing rapidly and with extensive hemopericardium pressure symptoms may be extreme and a condition called cardiac tamponade or acute constrictive pericarditis results These pressure symptoms are of two sorts those due to compression of the heart whereby insufficient blood enters the heart the lungs and the systemic arteries with resulting dyspnea weakness faintness venous congestion and epigastric and right upper quadrant discomfort from hepatic engorgement and those due to compression of lungs trachea bronchi esophagus and great vessels with further dyspnea or orthopnea irritative cough hoarseness and dysphagia Distressing dyspnea and thoracic oppression are common symptoms of a large pericardial effusion and the patient often assumes a characteristic attitude of distress sitting upright and leaning forward

**Signs** The signs of acute pericardial disease like the symptoms are due first to the fibrinous exudate and second to the effusion The characteristic sign of acute pericarditis often found at some stage of the disease is the *friction rub* but in many cases (over 75 per cent) it is absent or escapes notice (Cabot 1926 a friction rub was heard in only 40 or 21 per cent of 186 cases of acute pericarditis) It may be heard anywhere over the precordium and sometimes when marked even in the back or neck but it is commonest along the left border of the sternum It is usually rough and grating sounding near to the ear and increased by pressure of the stethoscope but sometimes it is so soft and gentle that it is distinguished with difficulty from heart murmurs It is heard as a rule both in systole and in diastole especially in the earlier parts of each but it may be almost continuous or it may be very brief and limited to systole alone being heard perhaps during only one phase of respiration It may be transient lasting but a few hours or it may persist with little change for weeks It is often audible even in the presence of an effusion but sometimes it disappears or is dulled when an effusion develops The pericardial friction rub if marked can be felt as well as heard

The other characteristic signs of acute pericardial disease are those produced by an effusion An amount less than 150 cc is probably not discoverable by any method of examination since it produces no definite signs In fact effusions of less than 300 cc are usually missed clinically The presence of a pericardial

friction rub should cause careful search for early signs of an effusion which may appear with the friction rub or shortly after it disappears. The earliest sign is roentgenologic and consists of a bulging of the lowest corners of the heart shadow because of the collection of fluid at these points. It is especially well seen in the oblique views fluoroscopically. As more fluid gathers it tends to fill in the hollows and grooves of the heart and great vessels, rounding out their contours and obscuring and eventually abolishing the cardiac landmarks. This change, at first apparent by roentgen ray, is later found by percussion also. The cardiac shadow and area of dullness often rapidly increase with the accumulation of fluid, giving rise sometimes to an erroneous diagnosis of acute cardiac dilatation. The increase may be very great so that the effusion shadow and the area of dullness may extend to the left axilla (Figure 136). A characteristic change in shape of the effusion shadow occurs with change of position, the shadow in the recumbent position being globular and that in the upright position pyriform (pear shaped), often obscurely likened to the shape of a water bottle. This change of shape is of course due to the effect of gravity. It is sometimes of considerable value in distinguishing between pericardial effusion and marked cardiac enlargement. By fluoroscopy and teleroentgenography the heart shadow itself is almost invariably buried in the shadow of the pericardial effusion since the densities of heart and effusion are almost the same. The cardiac pulsation fluoroscopically may be much diminished or even absent. An obtuse right cardiohepatic angle of percussion dullness (Rotch's sign) is found with large effusions.

An early sign of the *cardiac tamponade* or *acute constrictive pericarditis* due to pericardial effusion is enlargement of the liver with tenderness on pressure. Slightly displaced downward the liver is engorged due to compression of the right atrium, great veins, and especially the mouths of the hepatic veins which open into the inferior vena cava caused by the resting of fluid in the pericardial sac on the diaphragm at the point where the inferior vena cava comes through. Prolonged and extensive blocking of the hepatic veins may give rise to ascites with or without slight edema of the legs, which is due to coincident obstruction to the blood flow in the inferior vena cava. With very extensive effusions and the resulting compression of right atrium and both superior and inferior venae cavae, general edema may occur, but this is neither common nor marked. Cyanosis of skin and mucous membranes is frequently found when the heart action is much obstructed and the jugular veins are frequently engorged with visible venous pulse in the upright position.

After the development of a considerable pericardial effusion, heart sounds and murmurs are often diminished and the friction rub may disappear. The blood pressure with small effusions is unchanged, but with large effusions the systolic pressure is decreased and the pulse pressure much diminished. With acute constrictive pericarditis the pulse pressure may drop to 20 cm. With very large effusions the radial pulse may almost entirely disappear and in fact sometimes does disappear during inspiration, which is usually labored. This exaggeration of the so-called paradoxical pulse is of some diagnostic

significance (see Chapter 8) The systemic venous pressure is often greatly elevated to 20 or 30 cm of water (normal 4 to 8 cm) Tachycardia is usual to make up for the small cardiac output per beat but arrhythmia is uncommon

The one other important sign (Ewart's sign) of a large pericardial effusion is due to compression of the left lung At the angle of the left scapula an area of variable size is frequently found over which there are dullness on percussion bronchial breathing and increased tactile and auscultatory fremitus (Ewart 1896) this may occasion an erroneous diagnosis of pneumonia Recently however it has been pointed out that in some cases at least the Ewart's sign in pericarditis is due to an associated pulmonary lesion in the left lower lobe (infarct or rheumatic pneumonia—Levine and Gevalt 1940) or more likely to an accompanying pleural effusion at the left base (as a part of a polyserositis—Gordon 1940)

Ewart described ten signs of pericardial effusion of which the eighth and tenth are as follows

Ewart William Practical Aids in the Diagnosis of Pericardial Effusion in Connection with the Question as to Surgical Treatment *Brit M J* 1896 I 717

*Eighth Sign The Posterior Pericardial Patch of Dulness* Whenever fluid is effused into the pericardium the normal resonance is modified at the left posterior base in a most definite way A patch of marked dullness is found at the left inner base extending from the spine for varying distances outwards usually not quite so far as the scapular (angle) line and ceasing abruptly with a vertical outer boundary Above its extension is also variable according to the size of the effusion commonly it does not extend higher than the level of the ninth or tenth rib and here again its horizontal boundary is abrupt Its shape there is that of a square and it is quite unlike that of any dullness arising from pleuritic effusion You will not experience any difficulty in identifying the patch in question Rather greater care in percussion is needed however to follow the dullness as it extends to the corresponding vertebræ and for a short distance also to the right of them For some time I had overlooked this extension which owing to the general resonance of the right base is one of partial dullness only When however the effusion is considerable the extension of the patch in the right chest may become almost absolutely dull

I wish time permitted me to discuss with you the significance and the probable mechanism of production of this singular and most helpful sign It is best I should confine myself on this occasion to practical points The value of this sign is that unlike many others it is very sharply defined and does not fit any other diagnosis When in a doubtful case all the signs observed in front support the diagnosis of effusion and this sign is also found we have then in hand complete and crucial evidence of the existence of fluid whilst when as sometimes occurs previous adhesion of the anterior surface of the heart to the chest wall renders diagnosis extremely difficult this help is invaluable and its place so far as I am aware cannot be supplied by any other available diagnostic method

*Tenth Sign The Posterior Pericardial Patch of Tubular Breathing and Egophony* Immediately below or slightly to the left of the tip of the left scapula a patch of about 2 inches in diameter presents well marked tubular breathing and

**ægophony** This sign although not so important as that of the patch of dullness is very commonly if not always present in cases of considerable effusion, and gives valuable confirmation to other signs. It has been described by other observers. The mechanism of its production is analogous to that suggested above and is doubtless connected with pressure on the bronchi descending to that district, and with partial collapse of the pulmonary tissues. It also occurs in pleural effusions.

Other signs such as fever and leukocytosis may or may not be present depending on the cause. If the acute pericardial disease, they are generally present at some time during the illness.

**Electrocardiography** is of distinct diagnostic value. Changes in the *ST* segments and *T* waves and low voltage of all complexes being frequently found with extensive acute pericarditis with or without effusion, the more marked the pericarditis the more abnormal the electrocardiogram, especially if there is a long drawn out course or a large effusion. The *ST* segment and *T* wave changes in the precordial and limb leads resemble to a certain extent those found in coronary heart disease, especially those in acute occlusion over the site of infarction, namely elevation of the *ST* segments with succeeding flattening or inversion of the *T* waves. There are however two distinct differences: (1) the same *ST* segment and *T* directions are usually consistently found in all three classical limb leads in contrast to their opposite directions in Leads 1 and 3 in myocardial infarction, and (2) the *QRS* waves are not affected as a rule in pericarditis as they tend to be after acute coronary occlusion. In the chest leads the *T* waves in acute pericarditis are often inverted. Sometimes the electrocardiogram returns to normal rapidly with subsidence of the acute pericarditis (Figure 137) but often some of the abnormality persists even though the patient feels well. The electrocardiographic changes in acute pericarditis have been ascribed to two factors: compression of the coronary arteries by effusion or exudate and involvement of the underlying myocardium, the latter is almost certainly the more important if not the only cause. An interesting electrocardiographic distinction between massive pericardial effusion and marked cardiac enlargement has been pointed out by Tung (1941): the duration of electric systole (*QT* interval) is normal in the former and prolonged in the latter.

Paracentesis of the pericardium may prove the presence of fluid when there is an effusion, but such confirmation is unnecessary except when pus is suspected or the procedure is an essential part of treatment.

With air and fluid together in the pericardium a tinkling splash may be heard with each heartbeat.

**Course and prognosis** Acute pericardial disease generally occurs either as a benign illness discovered on occasion in the course of a fever and clearing spontaneously without sequelae in the course of days or weeks or as a passing complication of some infection like rheumatic fever or other illness like uremia or cardiac infarction. It may not be of great importance in itself, the fibrinous or serofibrinous involvement subsiding spontaneously or occurring

simply as a terminal event in a fatal disease. Frequently the pericarditis does not even produce symptoms or signs but is discovered only at postmortem examination. There are however three conditions in which the acute pericardial involvement is itself of great immediate importance. One is the infrequent very serious purulent pericarditis which is usually secondary to disease elsewhere and may be fatal unless there is ample surgical evacuation and drainage of the pus together with specific penicillin or sulfonamide therapy and good resistance on the patient's part. The second is a pericarditis that initiates a grave miliary tuberculosis. The third is more frequent viz. a large pericardial effusion generally of tuberculous origin but sometimes of rheumatic or of unknown etiology which causes serious pressure symptoms and signs (acute constrictive pericarditis) and which may endanger life unless it is aspirated. But as a rule drainage is unnecessary in acute pericardial disease.

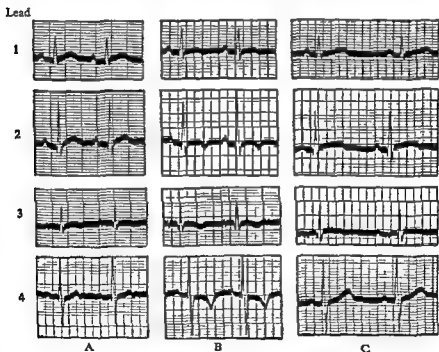


FIG 137 Electrocardiograms (four leads) of H C a lad of 12 years of age at the beginning of during and after recovery from acute pericarditis (A) Sept 4 1942 (B) Sept 8 1942 (C) Sept. 25 1942 Note especially the late inversion of the T waves in B

The onset of acute pericarditis is likely to be rapid but it is often masked by the underlying illness and not considered until discovered in the course of physical examination or roentgen ray study. Occasionally pain calls attention to an acute pericarditis which seems to appear out of a clear sky. The duration of the pericardial involvement in its acute stage varies from a few days to

a few weeks but chronic pericarditis may result. Such chronic pericarditis may cause no trouble at all or it may produce symptoms and signs after the lapse of some months or years.

The immediate prognosis in acute pericarditis is good as a rule in the non-pyogenic and nontuberculous infections in spite of well marked symptoms and signs but the total mortality is still fairly high because the term "acute pericarditis" includes the terminal pericarditis of uremia and overwhelming septic infections, occasional cases of fatal cardiac infarction and rare cases of death due to the mechanical effect of a huge or rapidly developing effusion. The introduction of penicillin and sulfonamide therapy has materially lowered the mortality in the cases with septic pericarditis during the last few years (see below under Treatment). Tuberculous pericarditis is often fatal; of one series of 24 cases of proved tuberculous pericarditis admitted to the Vanderbilt Hospital in Nashville, Tennessee during a period of eleven years only 4 survived (Blalock and Levy 1937) and analyses of other series of cases by Keefer (1937) and by Heimann and Binder (1940) have also indicated a generally poor prognosis although streptomycin has apparently been helpful or even curative in a few cases and it is also quite possible that cases too mild to diagnose may recover or lead to chronic constrictive pericarditis.

Hydropericardium, a part of general anasarca due to heart failure or nephritis, is not an important condition in itself; the course and prognosis are naturally depending on the underlying disease; it does not become large enough to constrict the heart.

**Complications.** The acute pericardial disease is itself but a complication of infections such as rheumatic fever and tuberculosis or of other diseases like uremia and coronary thrombosis. It rarely produces complications of its own except for the establishment of pericardial effusion and adhesions. Pleuritis may follow pericarditis by contact infection though usually the reverse is the sequence. Commonly associated with acute pericarditis are nephritis, valvular disease and polyserositis.

**Treatment.** The treatment of acute pericardial disease is wholly that of the underlying cause—rheumatic fever, tuberculosis, purulent pericarditis, coronary thrombosis or other disease—except for two conditions, pain and very large pericardial effusions.

Pain should be relieved by morphine when it is very severe; for lesser grades of pain salicylates, bromides or codeine may suffice. An ice bag placed comfortably over the precordium may be received gratefully by the patient.

The pain of acute rheumatic pericarditis is often much relieved by salicylate administration which probably also helps in the resolution of the acute process including the effusion.

For acute tuberculous pericarditis streptomycin has been tried during the past few years with benefit in some cases by injection intramuscularly (1 to 2 gm daily) and also by intrapericardial instillation although of course with the risk of labyrinthitis.

If pericarditis develops in the course of a pyogenic infection or following it and is itself the cause of prolongation of the illness or of accumulation of per-

cardial fluid exploratory paracentesis should be done as soon as possible or better still to save time and the patient's strength surgical pericardiostomy if the diagnosis of purulent pericarditis seems reasonably certain Equally important is the administration of penicillin 300 000 units daily or the sulfonamides e g sulfadiazene 1 gm 4 to 6 times a day Cure is now possible in many such cases which in former days were rapidly fatal

If the pus is thick it will be necessary to use a large aspirating needle or trocar sometimes only an incision will permit ready removal of the pus The discovery of a definite purulent pericarditis demands surgical interference at once with drainage as in the case of empyema and care should be taken that the bottom of the pericardial sac be drained Recovery is possible in such cases if proper treatment is instituted early in the disease If in the development or course of a pericardial effusion symptoms or signs (especially a rapid fall in arterial and pulse pressure and a rapid rise in venous pressure) indicate the existence of a high and perhaps dangerous intrapericardial pressure (cardiac tamponade or acute constrictive pericarditis) the pericardium should be aspirated of at least several hundred cubic centimeters of fluid provided they are easily withdrawn without inducing disagreeable symptoms As much as 1 000 or 1 500 cc of fluid have been aspirated in some cases The removal of even a small percentage of a large effusion may suffice to relieve distressing orthopnea and thoracic and epigastric oppression hypotension and small pulse with the saving of life and induction of convalescence

Pericardial paracentesis may be done in several ways It is often convenient to employ a long needle of small or average caliber (1 mm) attached to a large syringe of 50 or 100 cc capacity by rubber tubing directly or through a three way connection which allows the fluid to be aspirated and discharged without disconnecting the syringe the direct connection is somewhat more convenient since the syringe can be easily removed and the fluid quickly ejected each time after the syringe has been filled the rubber tube being closed by finger or clamp pressure while the syringe is disconnected In rare cases a larger caliber needle (2 mm bore) may be necessary

The site at which the pericardium should be tapped need not be limited to one spot for at times the fluid is more or less localized by previous adhesions and in some cases it is more easily obtained in one place than in another Generally the best site to try first is the fifth left intercostal space 1 or 2 cm toward the sternum from the left outer border of percussion dullness and roentgen ray shadow and therefore in the case of a large effusion usually beyond the position of the apex or left border of the heart The skin and subcutaneous tissues should be anesthetized first conveniently with 2 or 3 cc of 0.5 per cent procaine (Novocain) solution using a small syringe and needle this local anesthesia which is often omitted or inadequately done is wise for two reasons in the first place for the comfort of the patient especially since two or more attempts are sometimes necessary before the effusion is reached and secondly for the greater convenience of the physician who does not need to hurry or to fear a sudden movement of the patient such as may occur if sharp pain is felt After a few minutes wait for the anesthesia to take



effect, the exploratory needle is inserted pointed back and inward toward the spine and forced slowly between the ribs until it is felt to penetrate the resistant pericardial membrane at a variable distance from the outer surface of the thorax depending on the thickness of the chest wall but averaging 3 or 4 cm in the nonobese adult male. When the pericardial sac is entered fluid may or may not be easily withdrawn depending on the thickness of the fluid, the caliber of the needle or trocar, the position of the trocar in relation to the fluid, and whether or not obstruction of the mouth or lumen of the trocar results from a fragment of fibrin or from pressure against heart wall or pericardial surface. If no fluid comes, the needle should be variously tilted, slightly withdrawn or inserted further, or completely withdrawn to be introduced again. Occasionally the heart itself is felt against the trocar and may move it at every contraction; this should not cause alarm for even perforation of the ventricular wall is not dangerous except in rare cases when the right ventricle or right atrium is badly traumatized or a large coronary vessel may be injured. If fluid is not found by paracentesis well out in the fifth left interspace, another trial may be made in the fourth or fifth interspace nearer the sternum or in the fourth interspace to the right of the sternum and just inside the right border of dullness or roentgen shadow. This last location is a favorable one when the effusion projects unusually far to the right. I have aspirated 600 cc of fluid from this site when adhesions prevented fluid accumulation to the left.

There are two other sites for pericardial paracentesis that have been tried and sometimes found favorable: the epigastrium and the left side of the posterior thoracic wall. The epigastric site is advantageous because it drains the lower part of the pericardial sac, but special anatomic knowledge and experience are necessary so that the needle will be directed upward at the proper angle as well as backward and inward. In this method the needle is inserted high up in the sharp angle between the ensiform cartilage and the left costal border and is pointed upward at an angle of about 30 to 40 degrees to avoid peritoneum and diaphragm, the pericardial sac being encountered at a depth of about 3 or 4 cm. The left posterior thoracic site is useful in rare cases in which fluid is not obtained by paracentesis in the usual positions but is almost certainly present as indicated by pulmonary pressure signs at the angle of the left scapula (Ewart's sign), provided one can rule out pulmonary consolidation or pleural effusion as a cause of the Ewart's sign, not always easy to do. With the left arm of the patient raised to move the scapula outward, the needle is inserted after local anesthetization in the seventh or eighth intercostal space in the midscapular line. Insertion to the depth of 5 to 8 cm should yield fluid from a distended pericardial sac. I have withdrawn 500 cc of pericardial fluid through the back, affording great relief to the patient when attempts through the anterior chest wall were unsuccessful and the need of pericardial paracentesis was urgent. There is no danger of pleural or lung infection by this procedure unless purulent pericarditis is present in which case this site for the paracentesis should of course be avoided.

Aspiration of the pericardium usually does not have to be repeated either

the serous effusion soon subsides or operation with drainage, is carried out for purulent pericarditis. In a few cases however especially those of tuberculous origin it may be necessary to aspirate several times usually at intervals of a week or two or in severe cases at intervals of a few days.

Sometimes the pericardial sac is partially filled with air intentionally after fluid has been removed (Figure 136 page 712) with the idea of allowing resolution of the acute pericardial inflammation to occur with less likelihood of the formation of crippling adhesions during convalescence but this procedure has not yet proved to be particularly successful.

Acute pericardial tamponade due to hemorrhage from trauma needs rapid relief by surgery to repair the heart wound along with transfusion of whole blood. Intravenous infusions have been found beneficial preoperatively in acute pericardial tamponade (Cooper et al 1944).

**Differential diagnosis** Acute pericardial disease is often missed altogether because of absence or inadequacy of symptoms or signs predominance of the underlying disease or hasty or careless examination. There are four conditions which are most likely to be confused with acute pericardial disease (1) cardiac enlargement (2) acute myocardial infarction (3) the presence of harsh heart murmurs and (4) acute abdominal disease.

The fast development of pericardial effusion the frequent presence of a friction rub and the absence of particular reason for sudden cardiac dilatation generally distinguish without difficulty pericardial disease from cardiac enlargement but in some cases the distinction is impossible and in still other cases there is a confusing combination of pericardial effusion and cardiac enlargement in the same individual. The electrocardiogram is often helpful in the differentiation.

The frequent possibility of the confusion of acute infectious pericarditis especially the idiopathic kind in young male adults with cardiac infarction has become increasingly evident of late years and the importance of this error especially as regards prognosis can hardly be overemphasized. The prolonged and often severe precordial pain fever leukocytosis pericardial friction rub and common appearance of abnormalities in the electrocardiogram in acute infectious pericarditis may easily simulate the findings in acute cardiac infarction. There are certain clues however in the differentiation of the two conditions chief of which is the fact that infectious pericarditis itself is almost invariably painful with much aggravation of the pain on inspiration due in part to the common coexistence of a pleuritis (in fact the process is as a rule really a pleuropericarditis) while the pericarditis associated with myocardial infarction is per se (being visceral) painless the severe pain of the muscle involvement being uninfluenced by respiration and subsiding as a rule by the time the friction rub appears. Other clues are the difference in the electrocardiograms (see above) the frequent development of some degree of pericardial effusion and the younger age of the majority of the cases of acute pericarditis.

Very rarely does the character of the pericardial friction rub resemble that

of a heart murmur but it may be necessary in a few cases to wait to see if the uncertain sound persists disappears or becomes more definitely one thing or the other

Pain of acute pericarditis referred to the abdomen or hepatic engorgement due to an acute or subacute pericardial effusion may occasion a mistaken diagnosis of acute abdominal disease especially in children laparotomy has been done in some such cases for supposed acute appendicitis or other lesion

Rare causes of mistaken diagnoses include localized or encapsulated pericardial effusions which may be taken for aortic aneurysm mediastinal tumor or dilated left atrium, a pleural friction rub may be wrongly called pericardial. Careful study generally simplifies the differentiation

## B CHRONIC PERICARDITIS INCLUDING CHRONIC CONSTRICTIVE PERICARDITIS (PICK'S DISEASE)

One of the most difficult of all clinical cardiovascular diagnoses is that of chronic pericarditis. Fortunately it is for the most part of little or no importance. Frequently it produces neither symptoms nor signs.

**Etiology Cause** The causes of chronic pericarditis are acute pericardial inflammation of rheumatic tuberculous septic or other often unknown infectious origin and cardiac infarction (from coronary thrombosis) neoplasms and hemopericardium from trauma. The commonest known cause is the rheumatic infection and next comes pulmonary and pleural disease. Often the cause is obscure the antecedent acute inflammation having escaped notice. On occasion tuberculosis pneumonia polyserositis (Concato's disease Concato 1881) and the influenzal infection and rarely some septic infection are known to be responsible for chronic pericarditis. Trauma resulting in hemopericardium may leave chronic adhesive pericarditis.

At the Mayo Clinic (Smith and Willis 1932) 144 cases of chronic adherent pericarditis were found among 373 cases of pericardial disease (38.4 per cent), rheumatic fever was apparently the etiologic factor in 21.5 per cent pulmonary and pleural disease in 17.4 per cent cardiac infarction in 6 per cent neoplasms in 2.8 per cent and tuberculosis in 2.1 per cent while in the remainder (50.0 per cent) the cause was not evident.

**Age** Although the greatest incidence of this pathologic condition is in middle age chronic pericarditis may exist at any age between 10 and 60 years. The average age is about 35 years.

**Sex** Males are more often affected than females in the ratio of 2 or 3 to 1.

**Pathology** Following acute pericarditis of slight degree the healing process may leave but little thickening or scarring on more or less extensive areas of the pericardial surface without adhesions between the surfaces (parietal and visceral) but when the active process is extensive or of long duration adhesions of considerable extent result. Thus chronic pericarditis may be divided pathologically into five groups. First there is simply slight scarring consisting of thickening and fibrosis of the pericardial surface usually in small areas

without adhesions and without any effect on heart size or function. The well known milk spots or soldier's patches probably belong in this category although their etiology is obscure. As a matter of fact pericardial milk spots are common about one third of all persons over a year old showing them at autopsy (Nelson 1940) they are scarce in children but very common in old age. Two thirds of individuals with chronic valvular disease have them and half of those with coronary heart disease. *Second* there are slight loose localized pericardial adhesions of fibrous tissue also without effect on the size or function of the heart. *Third* there are the cases of complete but not dense adhesion between the visceral and parietal pericardial surfaces without firm fixation to chest wall diaphragm or mediastinum. In such cases the adhesions are often loose and the pericardium is but little thickened so that there is no handicap to the heart in its function and no cardiac enlargement. *Fourth* there is *concretio cordis* (a hardening of the heart) when the pericardial adhesions are solid thickened and even calcified. For such instances in which the heart function is impeded and the inflow of blood from the great veins obstructed (Figure 138 page 724) the best designation is *chronic constrictive pericarditis*; this condition may follow a polyserositis of unknown cause it may result from pneumonia but in most cases it is probably of tuberculous origin. Rarely the visceral and parietal pericardial layers may be densely thickened and unyielding but without complete adhesion. Often in these cases the heart is adherent to the diaphragm a further handicap. *Fifth* the adhesive pericarditis may be complicated by an extension of the process to the mediastinum and chest wall so that the heart itself is anchored in every direction by firm fibrous tissue (*chronic mediastinopericarditis*) with much extra work and some enlargement of the heart resulting.

The factors responsible for the fourth and fifth groups that is constricting and anchoring adhesions are often present in the same case. In fact it is usually difficult or impossible to separate these two groups the fourth and the fifth in general they might best be considered as one although there are exceptions. The only important cases of chronic adhesive pericarditis demanding especial attention belong here.

Occasionally lime and rarely even bone are deposited in chronic pericardial adhesions when they are especially thick and massive.

It is of much interest that long before Pick (1896) and even before Kussmaul (1873) the effect of chronic constrictive pericarditis on the heart and circulation was well understood by Chevers (1842) and Wilks (1870) at Guy's Hospital in London.

Chevers N. Observations on the Diseases of the Orifice and Valves of the Aorta  
*Guy's Hosp Rep* 1842 VII 387

The principal cause of dangerous symptoms in cases of the above description [with much thickened constricted pericardium and obliterated sac] appears to arise from the occurrence of gradual contraction in the layer of adhesive matter which has been deposited around the heart compressing its muscular tissue and

embarrassing its systolic and diastolic movements but more particularly the latter. Under these circumstances the circulation seems after a time in great measure to adapt itself to the encumbered condition of the heart. The ventricles having become diminished in capacity make up for this loss by the rapidity of their contractions (hence the small and rapid pulse noticed in the above case) while the main arteries if not already diseased adapt themselves to the dimensions of the



FIG 138 Photograph of heart encased in a thickened leathery constrictive pericardium. Case of chronic constrictive pericarditis (so-called Pick's disease)

cavities from which they arise. And thus the blood passes onward for a time with tolerable freedom but the patients become incapable of continued muscular exertion and are always liable to suffer from dropsy and other serous effusions upon the occurrence of very slight pulmonary obstructions. In the case which I have quoted the serous effusions which gave rise to the most prominent symptoms of disease evidently arose from the cavities of the heart being no longer capable of transmitting the blood with ordinary freedom. The heart had doubtless for a long time continued to become more and more compressed weakened and embarrassed by the gradual contraction of the adventitious structure which surrounded it. distension of the great veins and abdominal viscera had necessarily followed and the resulting anasarca and ascites must have added still more to the obstruction with which the already almost powerless heart had to contend.

Chronic mediastinopericarditis may be at times very complicated causing obstruction of the great veins the superior vena cava inferior vena cava and even the hepatic veins by linking and compression but particularly constriction and anchoring of the heart chambers themselves. It is the hepatic vein obstruction secondary to the constriction of the heart itself with or without an additional factor of local blocking that leads to hepatic congestion enlargement and eventual cirrhosis called *mediastinopericarditic pseudocirrhosis of the liver* or *Pick's disease* (Pick 1896). It should be added that this last named condition may or may not be associated with polyserositis (Concato's disease) and perihepatitis (icing or frosting of the peritoneum over the liver due to chronic peritonitis) these two different conditions that is mediastinopericarditis and polyserositis have often been confused in the past since it is true that the former condition may result from the latter. Chronic mediastinopericarditis may involve the superior vena cava even more than the inferior vena cava in cases of the superior mediastinal (pressure) syndrome but usually the inferior vena cava and hepatic veins are equally or more affected (inferior mediastinal syndrome) as a matter of fact the condition is usually a total mediastinal syndrome. The right heart chambers are more often seriously constricted than are the left heart chambers though there are many exceptions. The liver rarely shows more than vascular congestion with very little cirrhotic change a few cases progress to or are complicated by a moderate degree of hepatic cirrhosis. However there are seldom if ever the marked changes found in the usual cases of portal cirrhosis.

Pick F. Über chronische unter dem Bilde der Lebercirrhose verlaufende Perikarditis (perikarditische Pseudolebercirrhose) nebst Bemerkungen über die Zuckergussleber (Curschmann). *Ztschr f klin Med* 1896 **XXIX** 385

Pick described three cases (including the postmortem examination) of what he called pseudocirrhosis of the liver resulting from chronic adhesive pericarditis involving the mediastinum. The sex and age of these three cases were as follows: male of forty seven years, male of twenty six years and male of twenty four years. In the third case tuberculosis was the etiologic factor behind the pericarditis; in the second case tuberculosis was the probable factor and in the first case the cause was unknown.

His first sentences and his conclusions I have translated as follows

To differentiate clearly between primary and secondary disease of the liver is very difficult in occasional cases where liver enlargement with more or less ascites eventually leads to cirrhosis. This is especially the case if there are no well marked physical signs of a heart lesion or of circulatory stasis in the upper part of the body

#### Conclusions

1 There is a symptom complex of *pericarditic pseudocirrhosis of the liver* which is deceptively similar to one of the mixed forms of hepatic cirrhosis with enlarged liver and considerable ascites but no jaundice. This pseudocirrhosis of the liver is caused by disturbances of the circulation of the liver due to latent pericarditis. These circulatory disturbances lead to an increase in connective tissue (fibrosis or cirrhosis) which in turn causes stasis in the portal circulation with marked ascites

2 This symptom complex is found preponderantly in young individuals but it may be observed also in later periods of life

3 The following points are important in the differential diagnosis (a) absence of an etiologic factor for cirrhosis of the liver (b) history of a previous pericarditis and (c) earlier occurrence of edema of the legs. Certainty can come only through subsequent examination of the heart

**Symptoms** There may or may not be symptoms from chronic pericarditis. Usually there are none since cases of the first three unimportant pathologic groups discussed above are much more frequent than of the last two important groups. Clinically chronic pericarditis may be divided into four groups (1) that with unimportant adhesions or none at all which comprises the first three pathologic groups (2) that of an important degree of constrictive pericarditis without external adhesions (3) that of significant external adhesions to chest wall and mediastinum with little or no constriction of heart or great veins and (4) that of groups 2 and 3 combined to a greater or lesser degree. It is unlikely that from uncomplicated external pericardial adhesions per se the heart is ever exhausted by the strain of tugging in the chest wall or of pulling up the diaphragm with each contraction when heart muscle failure develops in the presence of adhesive pericarditis there is always to be found other more adequate cause for the failure especially aortic or mitral valvular disease. The pericardial adhesions may of course add a minor burden in addition but it seems to be relatively unimportant. When on the other hand the heart is so compressed that there is insufficient blood flow activity is usually much limited abdominal discomfort and distention result from hepatic congestion and ascites and there may be also dyspnea and weakness

**Signs** As is the case with symptoms so there may be no signs whatsoever of chronic pericarditis unless the pericardium is extensively adherent or constrictive. The usual absence of important adhesions clearly explains why the diagnosis is so often missed during life

A frequent finding in chronic adhesive pericarditis is cardiac enlargement but this is inconstant and not diagnostic and almost always there are other lesions especially valvular defects that are much more important causes of

the enlargement Cardiac enlargement is not present unless extra work has been required of the heart because of adhesions to chest wall diaphragm or mediastinum The enlargement is due to a combination of hypertrophy and dilatation Years ago it was reported (Cabot 1926) that the largest hearts of a certain series of cases were the result of chronic pericarditis but a careful survey of these cases showed that aortic valve defects (and not the pericarditis) were the real cause of the enlargement (White Sprague and Jones 1926) Increased heart size was found in 29 (55 per cent) of a series of 53 cases of chronic constrictive pericarditis (Paul Castleman and White 1948)

There are two signs which are more or less distinctive of chronic pericarditis of the more serious types The first is the fixation of the heart by adhesions in some cases physical examination and roentgen ray study show little or no change in the position of the heart with change in body position (upright recumbent right lateral position left lateral position) or respiration (full inspiration and full expiration) Electrocardiography is of least value in studying the extent to which the heart is anchored (see Chapter 9) Fixation of the heart to the sternum causes the heart to rise rather than to descend with inspiration with retraction of the lower end of the sternum at the same time Also the fixation of the heart and pleural edges may prevent any change of pulmonary resonance over the heart between full inspiration and full expiration The pleural edges are at times somewhat retracted from over the heart increasing the area of absolute percussion dullness Such definite fixation is however found in relatively few cases Other confirmatory signs of extensive pericardial adhesions are inconclusive in themselves they include especially a systolic retraction of the chest wall particularly in the left axillary region and left back involving the ribs as well as the intercostal spaces (Broadbent's sign) and probably due to fixation of heart to diaphragm Although this sign is sometimes also seen when the heart especially the right ventricle is very large without any adhesions it is seen best in cases of adherent pericardium

Broadbent John F H *Adherent Pericardium* London 1895

In Chapter II the section on Physical Signs of Adherent Pericardium begins as follows

The physical signs differ according as the adhesions exist only between the two layers of pericardium or between the pericardium and chest wall or adjoining pleura as well In the latter case they are more numerous and distinctive and will therefore be first discussed

P 26 *Retraction of the Posterior Lateral Portions of the Thoracic Walls* In cases of adherent pericardium marked systolic retraction of some of the lower ribs on the lateral or posterior aspect of the thorax may sometimes be seen This phenomenon is best seen when the patient is sitting up in a good light and the movements of the chest are carefully observed from a short distance off first from the front and then from the lateral aspect When a pulsatile movement is seen over the lowest part of the left side of the chest posteriorly it may at first sight appear to be expansile On a more careful scrutiny it will be found that there is a tug on the false ribs during the cardiac systole and a sharp rebound during diastole



which can be felt as well as seen when the hand is laid flat upon the chest wall at the spot it is more marked when a deep inspiration is made it may be seen occasionally not only on the left side but also on the right especially if the patient leans over to the left

Here it is not possible that the heart can be directly fixed to the chest wall at the points of retraction by pericardial adhesions as the lung tissue intervenes but the explanation seems to be the following The heart is by means of the pericardium adherent not only to the central tendon of the diaphragm but probably also to a large area of the fleshy or muscular portion of the diaphragm and, it may be to the anterior thoracic wall as well as it contracts it drags upwards and inwards the less resistant fleshy part of the diaphragm towards the central tendon or anterior chest wall hence the points of attachment of the digitations of the diaphragm to the lower ribs and costal cartilages are dragged inwards and downwards It will always be found in such cases that the retracted positions of the chest wall correspond to the floating ribs or costal cartilages of the lower ribs at the points of attachment of the diaphragm (Systolic recession of the left subcostal angle and epigastrium does not necessarily imply the presence of pericardial adhesions)

The above is a most important diagnostic sign of adherent pericardium when present and is quite distinct from recession of the lower ribs in inspiration

The other important and distinctive finding on physical examination occurs in cases of constrictive pericarditis due to the small amount of blood that can enter and therefore leave the heart because of the cardiac compression This finding consists of increase of systemic venous pressure even up to 20 or 30 cm of water (normal 6 to 8 cm) with engorged neck veins and hepatic engorgement (and in late cases slight cirrhosis), and ascites alone or out of all proportion to the degree of dependent edema in the legs (Figure 139) accompanied by low arterial pulse pressure often so small that the radial pulse almost disappears on deep inspiration (marked paradoxical pulse) This evidence is the clearest indication that we possess of an important degree of chronic pericarditis when linked with the finding of a relatively normal heart without valvular disease with little or no enlargement and with limited diastolic excursion as noted by roentgen ray study The pulsation of the right heart border is more often embarrassed than is that of the left

There is one sign a rare one which is pathognomonic of chronic pericarditis and that is the evidence by roentgen ray of calcification of the pericardium (Figure 140 page 730) Pericardial calcification may or may not be attended by constriction of the heart it was present in 29 (55 per cent) of 53 cases of chronic constrictive pericarditis (Paul Castleman and White 1948) Roentgen ray examination also infrequently shows actual irregularities of the contour of the cardiac shadow due to the pull of adhesions

Very helpful confirmatory evidence of chronic constrictive pericarditis is electrocardiographic There is invariably either low voltage of QRS waves (60 per cent) or inversion of T waves (all cases) or both (Figure 141 page 731) These abnormalities are also frequently found in cases of acute constrictive pericarditis

There are ordinarily no characteristic changes in heart shape and no murmurs or arrhythmias except as they develop as complications. A systolic murmur at the apex is frequent with enlargement and is due to functional mitral regurgitation. Very rarely there may be also a mitral diastolic murmur at the apex without mitral or aortic valve disease due simply to left ventricular

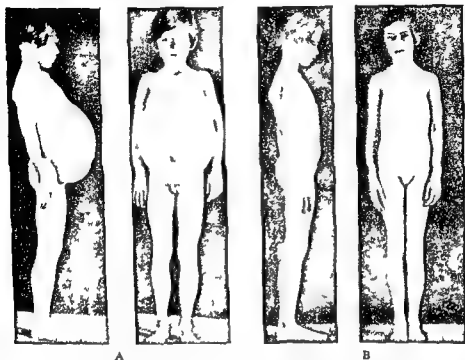


FIG. 139 : Photographs of young girl with chronic constrictive pericarditis (so-called Pick's disease) (A) during her disability (B) one and one half years after her surgical cure

dilatation resulting from the pericardial adhesions. A frequent finding in chronic constrictive pericarditis both before and after pericardial resection is a loud third heart sound especially well heard at the left lower border of the sternum which may be explained by right ventricular dilatation when the left heart chambers are more constricted than the right or the right ventricular myocardium weak and atrophic. Atrial fibrillation is common in the cases of chronic constrictive pericarditis (Pick's disease) and atrial flutter also may occur. These arrhythmias were present in 20 (38 per cent) of 53 cases of chronic constrictive pericarditis (Paul Castleman and White 1948). The blood pressure and pulse pressure are low if the blood flow is much reduced by the hampering of the heart action.

In a case with chronic constrictive pericarditis of long standing and attended by malnutrition the blood serum protein is often reduced to below 5 gm per cent and the albumin globulin ratio may be reversed favoring an increase in



FIG 140 Roentgenograms of thorax of GP age 45 with chronic constrictive pericarditis showing calcification of the pericardium (A) Anteroposterior view (B) right anterior oblique view

edema such a finding is due probably in part to the malnutrition in part to the loss of protein in the ascitic fluid and in part to the reduced liver function. There is usually but little anemia

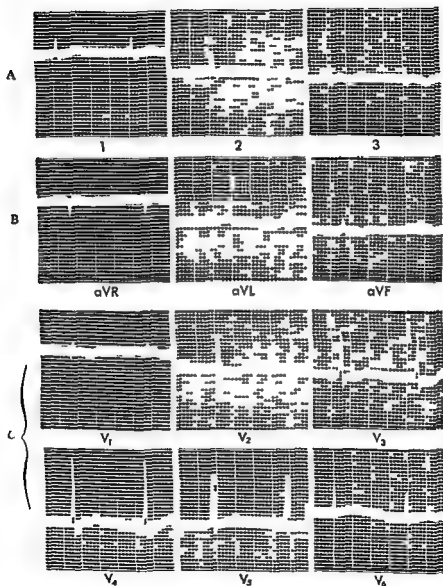


FIG 141 Electrocardiogram in chronic constrictive pericarditis male age 50 (A) Bipolar limb leads 1 2 and 3 (B) unipolar limb leads aVR aVL, and aVF (C) six precordial leads V<sub>1</sub> to V<sub>6</sub> inclusive Note especially the low voltage of the QRS waves in all the limb leads and the very low or inverted T waves throughout Despite the regular ventricular rhythm the P waves are not made out. Time = 0.04 and 0.20 second amplitude 1 mm = 0.10 mv

One of the most interesting varieties of chronic constrictive pericarditis which leads to pulmonary hypertension and right ventricular enlargement, acting much like mitral stenosis consists of preponderant involvement (constriction) of the left heart chambers, especially the left atrioventricular groove. Cardiac catheterization helps to confirm the pulmonary hypertension (White et al 1948), a special surgical approach can correct this as noted on page 735

**Course and prognosis** In the less important types of chronic pericarditis there is usually no interference with the normal duration and activity of life except as complications like valvular disease may affect the prognosis. In many cases the pericardial adhesions are discovered only at postmortem examination in patients who have never had any cardiac symptoms or signs and have died a noncardiac death. Even the original acute pericardial illness may be unsuspected or untraced. The more marked cases, however, especially those with constrictive pericarditis, generally develop symptoms and signs of heart failure or of systemic venous congestion with hepatic enlargement and ascites in youth. With crippled lives they may survive for many years but finally usually in middle age they gradually fail and die from the effects of the pericarditis itself or from complications unless they are relieved by pericardial resection which affords much help or even cure in about half the cases.

**Complications** The most frequent complications of chronic pericarditis have already been mentioned: systemic venous congestion with hepatic enlargement and ascites and chronic valvular disease (in about half the cases). Hypertension, coronary disease and bacterial endocarditis are infrequently associated with pericardial adhesions. Atrial fibrillation is found occasionally. Pleural adhesions are commonly associated with adhesive pericarditis; the result of a mutual polyserositis in the past, there may be chronic constrictive pleuritis as well as chronic constrictive pericarditis (Burwell and Ayer 1941).

**Treatment** There is no need of any particular treatment in most cases of adherent pericardium even if the condition is recognized, but there are two important surgical procedures, both called cardiolysis (*καρδια λυσις* to free) which are indicated in certain cases. These are (1) rib removal (thoracotomy) when there are extensive adhesions to the chest wall and (2) pericardial resection or cutting away of pericardium when there is compression of heart or great veins.

**Rib removal** The simpler chest wall operation called Brauer's operation (Brauer, 1902) consists of the removal of several ribs and costal cartilages (usually three) on the left side over the precordium for a distance of about 10 to 15 cm from the sternum. It quite probably can relieve the heart which is adherent to the chest wall of some at least of its extra work. This operation has also been suggested and done in rare cases of marked cardiac enlargement without pericardial adhesions to relieve the heart of the task of displacing the anterior chest wall forward at each systole, although it has not been generally adopted. Several patients have apparently experienced some subjective relief that is relief from the discomfort of the forceful heart action. The operation

has been performed but little for adhesive pericarditis and now has for that purpose been largely abandoned since the Delorme operation of pericardial resection has widely and justifiably supplanted it indeed in former days before the diagnosis of crippling chronic pericarditis was made with any degree of accuracy the Brauer operation was done in some cases that proved to have marked cardiac enlargement with no pericarditis at all

As a matter of fact freeing the heart from extensive adhesions to chest wall or diaphragm would be much better carried out in these modern days of enlightened thoracic surgery by splitting the sternum medially lengthwise without permanent deformity of the chest such as follows Brauer's operation

Brauer L. Ueber chronische adhesive Mediastino Perikarditis und deren Behandlung *Munch med Wchnschr* 1902 XLIX 1072

Die Erfolge der Kardiolyse *Ibid* p 1732

Two discussions of cardiolyse for adhesive pericarditis took place at the *Natur historischmedizinischer Verein in Heidelberg* May 13th and July 18th 1902 The official report of the first of these two sessions is as follows (the translation is by myself)

The speaker [Brauer] demonstrated two cases of chronic adhesive mediastino pericarditis and described in relation to these cases the etiology and diagnosis along with the expected further course and the pathologic structural changes doubtless present

Both patients showed in the most striking manner a systolic retraction of the lower anterior chest wall alternating with a vigorous diastolic rebound A collapse of the cervical veins was also evident during cardiac diastole The diastolic rebound of the chest wall was accompanied by a ringing tone which masked the usual second heart sound Kussmaul's signs of the pulsus paradoxus and of inspiratory dilatation of the neck veins were absent

In both cases there were signs of myocardial disease with enlargement of the liver and evidence of massive circulatory stasis

Since a significant increase of the work of the heart was caused by the systolic pulling in of the chest wall which rebounded immediately in diastole with so much force the speaker decided to free the heart by making a break in the bony ring of the thorax by the resection of ribs Through this procedure the heart would contract with the pulling in no longer of the elastic ribs but simply of a covering of the soft parts of the chest wall

Professor Petersen had happily brought about this result in one of these two patients by resecting the ribs covering the heart

The consequence of this operation described above and carried out on the first day of April 1902 was very satisfactory The patient is both subjectively and objectively much improved Similar treatment in the case of the second patient will therefore be considered

At the second session in July the following report was made

Following his intention at the assembly of the 13th of May 1902 (this journal No 25) the speaker [Brauer] demonstrated the second of the two patients shown previously

Dr Simon had performed the operation on this patient which the speaker

had recommended. This time a considerable part of the sternum was resected with the ribs.

The expected result followed. The patient whose heart no longer was obliged to pull in the entire anterior bony chest wall with each contraction but only a yielding surface improved appreciably. found that he could move more freely with less dyspnea and was almost completely rid of signs of cardiac insufficiency which had been threatening him.

Brauer L. Die Kardiolyse und ihre Indikationen. *Arch f klin Chir* 1903 LXXI 258

(Translation by myself.)

About a year ago I described under the name of cardiolyse a method for the surgical treatment of adhesive mediastinopericarditis.

Today I hope to be able to demonstrate to you the expediency of the procedure through the progress of both the cases which were reported at that time. In the meantime since the early reports a third case has been operated upon and new observations have been made on the differential diagnosis and the determination of those cases which qualify for the operation.

Moreover since one of the patients died a year after the operation from the accidental complication of an influenzal pneumonia the opportunity has been afforded to orientate the characteristics of the disease picture with the actual anatomical preparation and to discuss the different possible operative procedures.

The most important indication for cardiolyse is afforded by those forms of adhesive pericarditis which cause a systolic retraction of a broad area of the thorax. So long as vigorous thoracic movements of this sort are demonstrable a good result may be expected.

Finally with what aim should one operate? Is it necessary actually to free the adhesions or sufficient merely to restore freedom of action for the heart by simply resecting ribs or sternum? The former procedure has been recommended by Delorme and by Beck [New York] but apparently it has not yet been accomplished. It appears to be a very extensive procedure and it may be questionable whether or not one should subject the patient to it at all. All this must first be ascertained through further cooperative work of surgeons and internists.

The apparent operative success reported by Brauer may have actually been due in part at least to the breaking of a constricting cuirass around the heart in the course of freeing that organ from the chest wall even though there was no specific decortication.

*Pericardial resection.* The other operation mentioned above by Brauer more truly a freeing of the heart or cardiolyse consists of precordial rib removal with resection of the left side of the sternum whereby the pericardium and heart are exposed followed by the actual cutting away of as much of the thick constricting pericardium from the heart surface as is possible at the time with the resection also of any constricting bands about the great vessels especially such as may involve the inferior vena cava under the sternum (Delorme 1898). An expert and experienced surgeon must be selected to undertake this difficult operation and anesthesia must be carefully admin-

istered The operation is better postponed if possible until after the acute stage of any tuberculous pericarditis The younger and fitter the patient the less is the risk and the more likely is marked improvement to follow

Delorme Professor Sur un traitement chirurgical de la symphyse cardiopericardique *Bull et mem d l Soc d chir d Paris* 1898 XXIV 918

(Translation by myself)

If the surgeon feels legitimate regrets in publishing a method of treatment which he has conceived but been unable as yet to apply on the other hand he risks the loss of the advantage of the original idea and the compromise of its application if he waits too long It is to avoid this last difficulty that I have resolved to speak to you of a surgical treatment of cardio-pericardial adhesions concerning which I deposited a confidential note in 1895 at the Academy of Medicine and the application of which I have been unable to effect despite repeated appeals to my colleagues of the medical services of the Val de Grace Hospital This treatment consists of the resection or destruction of the cardio-pericardial adhesions

Already a considerable number of striking cases of relief and cure following pericardial resection have been reported as in the case of the child shown in Figure 139 page 729 (Rehn 1920 Sauerbruch 1925 Churchill and White 1929 1930 White 1935 1942 with Harrison and 1948 with Alexander and Sweet and with Paul and Castleman Blalock and Burwell 1935 1941 Beck 1931 and 1943) Of our own series of 53 cases 42 were subjected to this operation 25 (60 per cent) were cured or much improved 16 patients died 6 as the result of the operation itself 5 from complicating diseases 4 from the pericarditis itself and one of unknown cause 7 of the 11 cases not operated upon were too ill for surgery and 2 others did not need it (Paul Castleman and White 1948) One of our cured cases is illustrated in Figure 139 page 729) In September 1950 Dr C S Beck of Cleveland kindly wrote to me of the results of pericardial resection in his series of 61 patients 38 patients (62 per cent of the entire group) were classified as clinically cured Ten others were somewhat improved and two cases showed no improvement One patient died on the table and ten others during the postoperative period or later

The further development of the surgical treatment of serious chronic pericarditis is a promising field for the future An important step forward has consisted of a new surgical technic consisting of a lateral thoracic approach allowing exposure of both back and front of the heart or better still of the splitting of the sternum which allows the chest to be widely opened with less later mutilation of the chest By either of these approaches important degrees of constriction of the left heart chambers can be cleared by posterior pericardial resection done prior to that over the anterior heart chambers such an approach is indicated when there is evidence of pulmonary hypertension as presented on page 732



Medical treatment of chronic pericarditis is obviously less hopeful although it may aid considerably in combating the complications especially the venous congestion due to chronic constrictive pericarditis. The treatment of congestive heart failure in cases of serious heart disease especially with valvular deformities complicated by chronic pericarditis with or without important external adhesions is discussed in Chapter 30. The medical treatment of venous congestion in chronic constrictive pericarditis may be briefly summarized as follows: limited activity with much rest; diet low in salt limited to 1 gm or less of sodium daily, diuretic drugs by mouth and intravenously exactly as for congestive failure (see Chapter 30) and paracentesis of abdomen and thorax as needed. When the blood serum protein is low a high protein diet is somewhat helpful. Digitalis in chronic constrictive pericarditis is ineffective in controlling the congestion though it is very useful in controlling the heart rate when there exists the occasional complication of atrial fibrillation at one time as in 1937 when the second edition of this book was published it was thought by some including myself that a slow pulse in this disease might actually be harmful and that a relatively fast pulse should help to compensate so far as the blood flow is concerned for the small output of blood per beat but careful observation during the past decade has shown this not to be the case most of the patients being considerably better with slower pulse rates under digitalis therapy than with rates approaching or exceeding 100 per minute.

Omentopexy (Talma operation) is contraindicated in chronic constrictive pericarditis since it in no way affects the fundamental condition.

To prevent the development of pericardial adhesions in the course of acute pericarditis injections of air and oil into the pericardial sac have been suggested and made but such procedures have not yet been proved useful.

**Differential diagnosis.** When chronic pericarditis with external adhesions produces any signs at all it must be differentiated from cardiac enlargement per se from any cause with or without congestive failure. This can be done in a few cases where the heart is clearly fixed in position and where other etiologic factors like hypertension and valvular disease are absent. When other causes are combined with chronic adhesive pericarditis to produce cardiac enlargement and failure it is usually easy to diagnose the other causes and to miss the pericarditis. Broadbent's sign may be misleading being found in some cases of marked cardiac enlargement especially of the right ventricle without adhesive pericarditis the retraction of the heart from the chest wall during systole simulating the tug of pericardial adhesions. And as noted above chronic pericarditis even with calcification may be present without any cardiac enlargement or constriction at all.

A previous history of acute pericarditis is naturally of great value in the diagnosis of pericardial adhesions.

Chronic constrictive pericarditis causing enlargement of the liver with ascites (Pick's disease) must be differentiated from true cirrhosis of the liver. This can usually be done easily there are two clearly distinguishable points.

both to be found in the case of chronic constrictive pericarditis (1) engorgement of the neck veins and (2) abnormality of the electrocardiogram

It is also to be remembered that marked chronic mitral stenosis with or without tricuspid valve disease may itself be a cause of chronic hepatic congestion but in such a case the mitral diastolic murmur and other evidences of the mitral stenosis and tricuspid insufficiency are present

The usually insidious onset the liver engorgement with preponderant ascites (as compared with dependent edema) the increased systemic venous pressure (as shown by the neck veins) with relatively normal heart and the abnormality of the electrocardiogram are the clues which in combination make the diagnosis of chronic constrictive pericarditis certain

Finally chronic constrictive pericarditis is not polyserositis although it may follow it

### C CONGENITAL PERICARDIAL DEFECTS

There are three types of pericardial abnormality of congenital origin all rare These are absence or defect of the parietal pericardium diverticulum or hernia and lack of attachment of the pericardium For a discussion of these and bibliography the reader is referred to Chapter 13

### BIBLIOGRAPHY

#### PERICARDIAL DISEASE CHRONIC MEDIASTINOPERICARDITIS

##### PERICARDIAL SURGERY

SEE ALSO REFERENCES IN CHAPTERS 13 CONGENITAL CARDIOVASCULAR DEFECTS

14 RHEUMATIC HEART DISEASE 17 TUBERCULOSIS 21 CORONARY HEART DISEASE AND MYOCARDIAL INFARCTION AND 23 NEOPLASMS AND TRAUMA

#### Acute Pericardial Disease

- Alston J M "Tuberculous Pericarditis as a Sole Tuberculous Lesion in an Old Man" *Edinburgh M J* 1928 XXXV 101
- Barach A L "Pericarditis in Chronic Nephritis" *Am J M Sc* 1922 CLXIII 44
- Barnes A R and Burchell H B "Acute Pericarditis Simulating Acute Coronary Occlusion" *Am Heart J* 1942 XXIII 247
- Bellet S and McMillan T M "Electrocardiographic Patterns in Acute Pericarditis Evolution Causes and Diagnostic Significance of Patterns in Limb and Chest Leads Study of Fifty-seven Cases" *Arch Int Med* 1938 LXI 381
- Bigger I A "Suppurative Pericarditis" *Ann Surg* 1939 CIX, 763
- Blalock A., and Levy H E "Tuberculous Pericarditis" *J Thoracic Surg* 1937 VII 13.
- Blatt M L and Greengard J "Pericarditis as a Primary Clinical Manifestation of Tuberculosis in Childhood" *Am J Dis Child* 1928 XXXV 631
- Boas E. P. and Ellenberg M "Rheumatic Pericarditis with Effusion Treated with Salicylates" *JAMA* 1940 CXV 345
- Cabot H C *Facts on the Heart* W B Saunders Co., Philadelphia 1926
- Camp P D and White P B "Pericardial Effusion A Clinical Study" *Am J M Sc* 193 CLXXXIV 782.

- Concato L Sulla Poliorromennite Scrofolosa o Tisi delle Sierose *Giorn internat d Sc med* 1881 III 1037
- Covsio P and Berconsky I Sarcoma primitivo pericardio miocardico *Rev Argentina d Cardiologia* 1938 V 172
- Cushing E H Diverticulum of Pericardium *Arch Int Med* 1937 LIX 56
- Ewart W Practical Aids in the Diagnosis of Pericardial Effusion in Connection with the Question as to Surgical Treatment *Brit M J* 1896 I 717
- Gordon A H (See reference Levine and Gevalt)
- Harrell G T and Johnson C Pericardial Effusion in Myxedema *Am Heart J* 1941 XXV 505
- Heimann H L and Binder E "Tuberculous Pericarditis" *Brit Heart J* 1940 II 165
- Keefer C S Tuberculosis of the Pericardium A Study of Twenty Cases" *Ann Int Med* 1937 X 1085
- Levine S A and Gevalt F C Jr with discussion by Gordon A H "The Significance of Ewart's Sign" *Tr A Am Physicians* 1940 LVI 100
- Marfan A B Le diagnostic des épanchements pericardiques et la ponction épi astrique du pericarde *Semaine méd* 1913 XXXIII 469
- Orgain E S and Poston M A Pericarditis with Effusion Due to the Meningococcus *Am Heart J* 1939 XVIII 368
- Pleble R B Etiology of Pericarditis *JAMA* 1901 XXXVII 1510
- Rotch T M Absence of Resonance in the Fifth Right Interspace Diagnostic of Pericardial Effusion *Boston M and S J* 1878 XCIX, 389 and 421
- Smith H L and Willis F A Pericarditis I Chronic Adherent Pericarditis II Calcification of Pericardium III Pericarditis with Effusion IV Fibrinous Pericarditis and Soldier's Patches V Terminal Pericarditis *Arch Int Med* 1931 L 171 184 192 410 and 415
- Stokes W Researches on the Diagnosis of Pericarditis *Dublin J M Sc* 1834 First Series Vol IV 29
- Stone W J Pericarditis as a Complication in Pneumonia Based on Three Hundred Necropsies" *JAMA* 1919 LXXIII 254
- Taylor J On Some of the Causes of Pericarditis Especially Acute Rheumatism and Bright's Disease of the Kidneys with Incidental Observations on the Frequency and on Some of the Causes of Various Other Internal Inflammations" *Med-Chir Tr London* 1845 XXVIII 453
- Tung C L The Duration of Electrical Systole (Q T Interval) in Cases of Massive Pericardial Effusion *Am Heart J* 1941 XXII 35
- VanderVeer J P and Norris R I "The Electrocardiographic Changes in Acute Pericarditis" *JAMA* 1939 CXIII 1483
- Vernay Sur le ponction du pericarde *Gaz hebdomadaire de médecine et de chirurgie* 1856 III 791
- Waldorp C P and Genjovich S "Pericarditis tuberculosa Estado actual" *Prensa méd Argentina* 1934 XXI 216

#### Recent References (1944-1950)

- Almansa de Cara B Consideraciones sobre algunos aspectos de la pericarditis tuberculosa y a su tratamiento con estreptomycin *Revista Espanola de Cardiol* 1949 III 441
- AnJensen W T "Pericarditis sicca juvenilis benigna" *Acta med Scandinav* 1948 CXXXI 47
- Auerbach O Pleural Peritoneal and Pericardial Tuberculosis Review of 209 Cases Uncomplicated by Treatment or Secondary Infection *Am Rev Tuberc* 1950, LXI 845
- Cachin M and Maurice P La péricardite myxoedémateuse *La Semaine des Il* 1950 XXVI 137
- Carmichael H B Sprague H B Wyman S M and Bland E F "Acute Nonspecific Pericarditis Clinical Laboratory and Follow up Considerations" *Circulation* 1951 III 321
- Coe H P A "Instillation of Streptomycin into the Pericardial Sac in Tuberculous Pericarditis" *Brit M J* 1951 I 18
- Cooper F W Jr Stead F A Jr and Warren J V "The Beneficial Effect of Intravenous Infusions in Acute Pericardial Tamponade" *Ann Surg* 1944 CXX 8

- Cossio P and Berconsky I: Pericarditis Aguda Benigna. *Medicina* 1947 VII 1
- Curti F C and Baroni V: Il trattamento della pericardite tubercolare con streptomina. *Rivista di Pat e Clin della Tuberc* Bologna 1949 XXII 288
- DeCarlo J Jr and Lindquist J N: "Angiocardiographic Observations of Patients with Primary Hemangiosarcoma of Pericardium." *Am J Roentgenol* 1950 LXIII 360
- Fischer J W: Neoplastic Involvement of Pericardium Producing the Syndrome of Constrictive Pericarditis. *Am Heart J* 1948 XXXV 813
- Griffith G C and Wallace L: The Etiology of Pericarditis. *Am Heart J* 1949 XXXVII 636
- Grossman C M: Pneumococcal Pericarditis Treated with Intrapericardial Penicillin. *New England J Med* 1945 CCXXXIII 689
- Harken D E: Removal of Foreign Bodies from Pericardium and Heart. Moving Picture Demonstration. *J Thoracic Surg* 1947 XVI 701
- Holman E and Willett F: Treatment of Active Tuberculous Pericarditis by Pericardiectomy. *JAMA* 1951 CXLVI 1
- Johnson R P and Bercu B A: Streptomycin in the Treatment of Tuberculous Pericarditis. Report of Three Cases. *Am Rev Tuberc* 1949 LIX 656
- Kern F Jr: Amebic Pericarditis. *Arch Int Med* 1945 LXXVI 88
- Schnitzer R and Gutmann D: Myxoedema with Pericardial Effusion. *Brit Heart J* 1946 VIII 25
- Williams R G and Steinberg I: The Value of Angiocardiography in Establishing the Diagnosis of Pericarditis with Effusion. *Am J Roentgenol* 1949 LXI 41

### Chronic Pericarditis

- Blalock A and Burwell C S: Thoracic Duct Lymph Pressure in Concretio Cordis. Experimental Study. *J Lab & Clin Med* 1935 XXI 296
- Borrmann A: "Über Polyserositis chronica fibrosa und verwandte Zustände (Ein Fall von Zuckergussdarm)." *Virch Arch f path Anat* 1927 CCLXIV 700
- Broadbent J F II: *Adherent Pericardium*. Tindall & Cox London 1895
- Burwell C S and Ayer G D: Constrictive Pleuritis and Pericarditis. *Am Heart J* 1941 XXII 267
- Cabot R C: *Facts on the Heart*. W B Saunders Co Philadelphia 1926
- Chevers N: Observations on the Diseases of the Orifice and Valves of the Aorta. *Guys Hosp Rep* 1842 VII 387 (First adequate description of chronic constrictive pericarditis)
- Finsen N R: Om Behandling og Forebyggelse af Ascites. *Ugeskr f Laeger* 1894 I 890
- Is there a chronic sodium chloride poisoning attendant upon a raising of the salt in the body? A research based upon observation and experiments on myself. *Ugeskr f Laeger* 1904 No 7 p 145
- Fløjstrup A and Scheel V: Niels R Finsens Sygdom. *Ugeskr f Laeger* 1904 No 43 p 1015
- Harrison M II and White P D: Chronic Constrictive Pericarditis. A Follow Up Study of 37 Cases. *Ann Int Med* 1942 XVII 790
- Hutinel: Cirrhoses cardiaques et cirrhoses tuberculeuses chez l'enfant. *Rev mens d mal d l'enfance* 1893 XI 529 and 1894 XII 15
- Kelly A O J: On Multiple Serositis—The Association of Chronic Obliterative Pericarditis with Ascites with Particular Reference to the Pericarditic Pseudo-cirrhosis of the Liver of Pick and the Iced Liver (Zuckergussleber) of Curschmann. *Am J M Sc* 1903 CXXV 116
- Kussmaul A: "Über schwierige Mediastino Pericarditis und den paradoxen Puls." *Berlin klin Wchnschr* 1873 Nos 37-39 pages 433 445 461
- Nelson A A: Pericardial Milk Spots. *Arch Path* 1940 XXIX 256
- Nigst P F: Fall von 250 Mal Punktiertem Aszites bei Pick scher perikarditischer Pseudolebercirrhose (Zuckergussdarm Leber Milz und Panzerherz) nach akuter Osteomyelitis. *Schweiz med Wchnschr* 1934 LXIV 966
- Pick F: Ueber chronische unter dem Bilde der Lebercirrhose verlaufende Pericarditis (pericarditische Pseudolebercirrhose) nebst Bemerkungen über die Zuckergussleber (Curschmann). *Ztschr f klin Med* 1896 XXIX 385
- Schmieden V., and Fischer H: "Die Herzbeutelentzündung und ihre Folgezustände." *Ergebn d Chir u Orth* 1906 XIX, 98

- Schur M. Probleme der adhesiven Perikarditis *Ergebn d inn Med* 1934 XLVII 548
- Smith H L and Willis F A Pericarditis I Chronic Adherent Pericarditis II Calcification of Pericardium III Pericarditis with Effusion *Arch Int Med* 1932 L 171 184 192
- Waldorp C P and Genjovich S *Enfermedades del Pericardio* Aniceto Lopez, Buenos Aires 1934
- White P D. Chronic Constrictive Pericarditis (Pick's Disease) Treated by Pericardial Resection *Lancet* 1935 II 539 597
- White P D Sprague H B and Jones T D. The Correlation of Clinical and Pathological Findings in Cardiovascular Disease *J Iowa State M Soc* 1936 XVI 479
- Wilks S. Adherent Pericardium as a Cause of Cardiac Disease *Guy's Hosp Rep* third series 1870-1871 XVI 196

#### Recent References (1944-1950)

- Andrews G W S Pickering G W and Sellors T H. Etiology of Constrictive Pericarditis with Special Reference to Tuberculous Pericarditis Together with Note on Polyserositis *Quart J Med* 1948 XVII 291
- Bishop L F Jr Kirschner P A and Pessar T. Diverticulum of the Pericardium. *Circulation* 1950 I 813
- Couter W T and Reichert R E Jr. Primary Systemic Amyloidosis Mimicking Chronic Constrictive Pericardial Disease *Circulation* 1950 II 441
- Falk A and Ebert R V. Tuberculous Pericarditis Treated with Streptomycin *JAMA* 1951 CXLV 310
- Froment R Gallavardin L and Cahen P. Chasquidos y vibraciones de las pericarditis constrictivas *La Semana M d* 1949 LVI 76
- Paul O Castleman B and White P D. Chronic Constrictive Pericarditis Study of 53 Cases *Am J M Sc* 1948 CCXVI 361
- Sawyer C G. Involvement of the Left Ventricle is of Primary Importance in Constrictive Pericarditis *J Clin Investigation* 1950 XXIX 843

#### Pericardial Surgery

- Beck C S. The Surgical Treatment of Pericardial Scar *JAMA* 1931 XCVII 84
- Blalock A and Burwell C S. Chronic Pericardial Disease Report of Twenty-eight Cases of Constrictive Pericarditis *Surg Gynec & Obst* 1941 LXXIII 433
- Brauer L. "Ueber chronische adhesive Mediastino Perikarditis und deren Behandlung" *Munch med Wchnschr* 1902 XLIX 1072 1732
- Churchill E D. "Decortication of the Heart (Delorme) for Adhesive Pericarditis" *Arch Surg* 1929 XIX 1457
- "Pericardial Resection in Chronic Constrictive Pericarditis" *Ann Surg* 1936 CIV 516
- Delorme E. "Sur un traitement chirurgical de la symphyse cardiopéricardique" *Bull et mem d l Soc d chir d Paris* 1898 XXIV 918 and *Ga d hop* 1898 LXXL 1150
- Rehn L. Die perikardialen Verwachsungen im Kindesalter *Arch f Kinderheilk* 1905 LXVIII 179
- Sauerbruch F. *Die Chirurgie der Brustorgane* Julius Springer Berlin 1925 Vol II.
- Volhard F and Schmieden V. Über Erkennung und Behandlung der Umklammerung des Herzens durch schwierige Perikarditis" *Klin Wchnschr* 1923 II 5
- White P D. "Chronic Constrictive Pericarditis (Pick's Disease) Treated by Pericardial Resection" *Lancet* 1935 II 539 597
- White P D and Churchill E D. "The Relief of Obstruction to the Circulation in a Case of Chronic Constrictive Pericarditis (Concretio Cordis)" *New England J Med* 1930 CCII 165
- Winkelbauer A and Schur M. Zur chirurgischen Therapie der adhesiven Perikarditis *Med Klin* 1935 XXXI 1231

*Recent References (1944-1950)*

- Harrington S W "Chronic Constrictive Pericarditis Results of Partial Pericardiectomy and Epicardiolysis in Thirty four Cases" *Mod Concepts Cardiovas Dis* 1947 XVI No 5
- Holman E and Willett F "Surgical Correction of Constrictive Pericarditis" *Surg Gynec & Obst* 1949 LXXXIX 129
- White P B Alexander F Churchill E B and Sweet R H "Chronic Constrictive Pericarditis Over Left Heart Chambers and Its Surgical Relief" *Am J M Sc* 1948 CCXVI 378

---

## CHAPTER 28

---

### VASCULAR DISEASE DISEASES OF THE AORTA AND PULMONARY ARTERY PULMONARY EMBOLISM ANEURYSMS DISEASES OF ARTERIES AND VEINS

---

Vascular disease like heart disease itself has seen a good many advances during the past seven years since the last edition of this book especially in the fields of diagnosis and surgical therapy but only the most important of these advances can find a place in this fourth edition

Blood vessel abnormalities make up an important part of the study of cardiovascular disease not only from the standpoint of the circulation as a whole but also from that of the heart itself Many vascular disturbances are of functional nature due to abnormal dilatation or constriction of arteries and capillaries and these will be discussed in Chapter 31 (Part IV Disorders of Cardiovascular Function) Structural vascular changes as they affect the heart and great vessels will be considered in the present chapter Diseases of the peripheral circulation per se however will be discussed but briefly in the present edition in order to save space in this expanding book which deals primarily with diseases of the heart and great vessels Many of the newer significant references to publications on peripheral vascular disease have however been added to the Bibliography and the reader is also referred to the newer textbooks on the subject

#### DISEASES OF THE AORTA

Organic disease of the aorta is exceedingly common but fortunately it is of little or no importance in the majority of cases Some change of the aortic wall is almost universal after the age of forty years

## ACQUIRED AORTIC DISEASE

**Etiology Cause** There are four chief types of acquired aortic disease (1) atherosclerosis the most common type (2) dilatation due to hypertension or aortic regurgitation (3) infectious changes and (4) rarely traumatic lesions. Besides these types there are occasional instances of aortic disease of unknown nature.

The first and commonest lesion called atherosclerosis is found in considerable degree in old age but begins often in youth. The cause of the abnormal deposition of cholesterol fat droplets and crystals in the intima of the aorta which constitutes atheroma is still unknown whether a fault in fat metabolism or of local tissue function or of other nature. Much study of these factors is needed to solve this very vital problem. Heredity is the only recognizable factor that is fairly consistent. It seems likely that several factors (especially heredity local strain and disturbed fat metabolism) may combine to cause atheroma.

Dilatation of the aorta of moderate degree is a common result of chronic hypertension and of well marked aortic regurgitation and in rare cases is due in old age to a loss of elasticity with resultant senile ectasia (*ectasis* a stretching out).

Infectious aortitis is frequently seen in youth and middle age most commonly and typically as a late manifestation of syphilis but it is also occasionally found as an acute lesion (called mycotic) in other infections such as rheumatic fever typhoid fever and tuberculosis. Saccular aneurysms are almost invariably the result of syphilitic aortitis.

Traumatic lesions the result of direct or indirect trauma (perforation blows strain) occur as a rule in the case of an aorta already diseased most commonly by syphilis atheroma or medial necrosis of unknown cause. If the trauma is indirect it occurs usually at the time of the greatest distention of the aorta.

Medial necrosis and hypertension combined with or without the additional element of trauma give rise in rare cases to a very important lesion consisting of a splitting of the aortic wall called a dissecting aneurysm.

**Age** Naturally the great preponderance of aortic disease is found in older persons after the age of 45 years because hypertension and syphilitic aortitis are then more advanced and because atheroma is especially a senile change. Atherosclerosis has however been noted frequently in otherwise healthy individuals between the ages of 30 and 50 years and sometimes even in children and youths. On the other hand the aorta especially in the ascending portion is often astonishingly smooth and elastic in individuals over the age of 75 years in fact this appears to be the rule in persons who live to be very old it may be evidence of the inheritance of good arterial tissue. Infectious aortitis is commonest in young and middle aged individuals syphilis being the chief factor between 40 and 50 years of age.



**Sex** The male sex is more often the victim of aortic disease than is the female in the proportion of about 2 to 1

**Pathology** *Atheroma* (αθήρη crushed grain or porridge) begins as a deposition of cholesterol fat in the intima where it appears engulfed in lipid

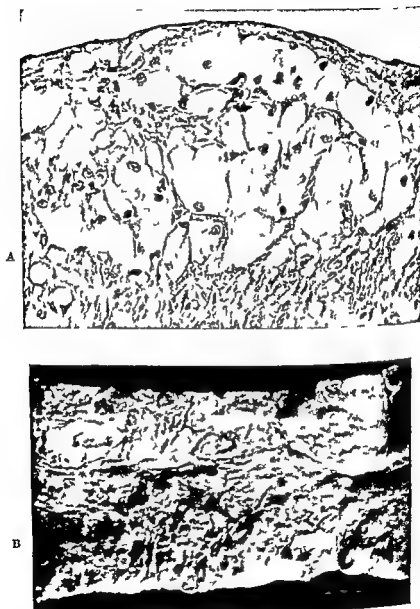


FIG 142 Photographs showing aortic atherosclerosis (A) Microphotograph showing atheromatous lesions of the aorta with cholesterol in the lipid cells grossly the lesion was a pinhead sized orange yellow nodule (kindness of Dr Timothy Leary) (B) Atherosclerosis of thoracic aorta showing well marked atheroma calcification and resulting ulceration (Jores *Arterien* kindness of Julius Springer Berlin)

cells (Figure 142A.) There are thus produced small fleck like areas which raise slightly the inner surface of the aorta encroaching a little on the lumen. This encroachment in the case of the aorta is of little or no moment but in very small arteries it becomes important. Gradually these areas tend to increase in size and number discoloring the aortic intima yellow. At first the process is reversible the fat being taken up and away but finally there is a reaction of fibrosis in these areas in middle age or even in younger persons while in older individuals lime salts are deposited in them in either case stiffening results to which the term sclerosis (*σκληρωσις* hardness) has been applied. The development of the whole process from softening to hardening has been called atherosclerosis. The aorta may eventually become more or less rigid and quite inelastic (Figure 142B.) The atherosclerosis may then be a handicap though not a serious one to the circulation which is normally maintained in part by the elastic pressure of the aorta when it is filled with blood by ventricular systole. The calcified areas or plaques may break or cause ulceration of the endarterium leading to intra aortic thrombus formation. The descending aorta in thorax and abdomen is more often involved by the atherosclerotic process than is the ascending aorta—for unknown reason but perhaps because it is less adequately supplied with vasa vasorum. Sometimes the descending aorta when it loses its elasticity becomes much elongated tortuous and even kinked (Roesler and White 1931) and has been known indeed to cause mild attacks of subacute intestinal obstruction (Palmer 1942) associated with the arteriosclerosis of the descending aorta especially the abdominal portion. Nonsyphilitic saccular aneurysms now and again occur. It has already been noted that in very old persons the aorta especially the ascending portion may be extraordinarily normal resembling that of a young adult.

*Infectious aortitis* is mainly of two types that in which the media or musculature is chiefly involved and that in which endarteritis is the primary lesion. Rarely invasion of the aortic wall occurs directly by extension of infection through the adventitia from contiguous lesions as in the case of tuberculous lymphatic glands pressing against the aorta. Slight infectious lesions may heal without causing any structural defect but there are six abnormalities of the aortic wall that more or less frequently follow aortitis especially of syphilitic origin. These six defects are (1) weakening of the aortic wall with loss of elasticity and dilatation (2) aneurysmal pouches (3) rupture of wall either partial or complete (4) ulceration of the intima (5) thrombus formation on the inner surface of the aorta usually over ulcerated areas and (6) partial or complete obstruction of the mouths of aortic tributaries—coronary innominate carotid subclavian and intercostal arteries. The extensive infectious lesions in which a large percentage of the aortic wall is involved are almost invariably syphilitic in nature in such cases the ascending aorta is the chief site of the disease beginning a short distance (1 or 2 cm) above the aortic valve the media is the coat affected with destruction of muscle and elastic tissue patchy whitening of the aortic surface with wrinkling and secondary involvement of the intima (Figure 89 page 412 compare with

Figure 142B) The syphilitic lesion probably results mainly from occlusion of the vasa vasorum but treponemata themselves are found in the aortic wall. Small localized aortic lesions are sometimes the early stage of syphilitic aortitis but often such lesions are due to other infection either directly involving the intima or through embolic invasion of the media by way of the vasa vasorum. Occasionally these localized aortic lesions are complications of bacterial endocarditis and infrequently they are seen in rheumatic infections typhoid fever and tuberculosis. There may result ulcerations small mycotic aneurysms and intra aortic thrombi resembling valvular vegetations which may contain bacteria.

In the case of syphilitic aortitis the infectious process may also progress downward to invade the aortic valve and to produce a serious aortic regurgitation (Figure 131 page 686).

*Medial necrosis* Small defects of the media of the aorta due to necrosis of unknown origin have become recognized as distinct from syphilitic or other well known infectious lesions (Erdheim 1929) they are apparently a factor in the production of dissecting aortic aneurysms.

*Saccular and dissecting aneurysms of the aorta* will be discussed later in the present chapter.

*Rupture of the aorta* is a common sequel of weakening of the wall and aneurysmal dilatation usually of syphilitic origin occasionally rupture results from dissection of the wall (dissecting aneurysm of the aorta) due to the combination of medial necrosis (of unknown cause) and hypertension or even without the hypertension it may occur as a complication of congenital coarctation of the aorta rarely rupture results from atheroma and in a few cases it is caused directly by trauma of a healthy aortic wall. The perforation may be very small consisting of a minute devious tear through the dissected aortic wall or of a tiny point at the bottom of an aneurysm with slow or intermittent bleeding in very rare cases spontaneous healing may take place with or without recurrence later. There may be a large linear tear often clean-cut as if with a knife especially when there is no previous aortic disease such a large tear results in a profuse rapidly fatal hemorrhage. Bleeding from aortic rupture is usually internal into pericardial sac pleural cavity, mediastinum or other great vessels (pulmonary artery innominate artery superior vena cava innominate vein) infrequently it is external into esophagus trachea bronchus or through the skin when the aneurysm has perforated the bony chest wall.

Spontaneous rupture of the diseased or weak aorta most often occurs during unusual exertion but it may take place at rest. Commonest is the rupture of a saccular aneurysm almost always syphilitic next most common is complete or almost complete transverse rupture a little above the aortic valve then there are tears in the inner and outer coats not immediately opposite each other and finally there are the dissecting aneurysms (Harris 1938). Occasionally there are incomplete aortic wall tears that are an accidental finding at autopsy (Perry 1942).

*Simple diffuse dilatation of the aorta* mainly of the ascending portion and arch common in chronic hypertension and aortic regurgitation is as a rule unimportant since the aortic wall may be otherwise normal with good muscle and elasticity if however there is in addition atherosclerosis medial necrosis or aortitis the hypertension or aortic regurgitation may be an important extra burden favoring the production of aneurysms and rupture. Extreme ectasia is rare.

*Effect of aortic disease on the heart* The heart itself may or may not show signs of involvement in the presence of disease of the aorta such involvement is either incidental due to coronary artery disease hypertension or valvular disease or it results from complications of the aortic disease such as syphilitic aortic regurgitation narrowing of the mouths of the coronary arteries or arteriovenous aneurysm by rupture of aorta into a great vein. Left ventricular enlargement is the chief finding in such cases.

Uncomplicated aortic disease does not cause any demonstrable change in the heart either functionally or pathologically.

*Symptoms* There are no definite symptoms of aortic disease except those which result from the most common complications (1) distress due to pressure from aneurysmal dilatations (2) excruciating pain from tearing of the aortic wall in the case of dissecting aneurysms and (3) angina pectoris or pain elsewhere in the body caused by occlusion of the mouths of the coronary or other arterial branches. Rare cases with slow bleeding from rupture may also have symptoms hemoptysis hematemesis weakness pallor. Involvement of the wall itself without aneurysmal pressure medial dissection or arterial mouth occlusion has been blamed as a cause of symptoms especially of pain often of the nature of angina pectoris but there is no proof that simple aortic wall involvement can cause pain. It is now quite certain that angina pectoris is a symptom of coronary insufficiency whether or not the result of narrowing or occlusion of the coronary mouths rather than that it is a symptom of aortic disease alone. Usually there are no symptoms at all from disease of the aorta.

*Signs* As in the case of symptoms so in the case of signs there is no evidence of slight structural disease of the aorta. Extensive involvement often of syphilitic nature produces signs mostly dependent on dilatation of the aorta (Figure 143 over). Dilatation due to hypertension may also be visible by roentgen ray examination (Figure 96 page 476). Atherosclerosis if extensive results in an elongation and tortuosity of the aorta due to loss of elasticity this tortuosity with prominence of the aortic knob (uppermost curve of the arch to the left) evident by roentgen ray study is a very common finding in old age (Figure 144 page 749). Advanced atherosclerotic changes with calcification in the aortic wall make the roentgen ray shadow of the aorta more dense than normal.

Roentgenology continues to be the most important means of detection of aortic disease for it is only when dilatation of the ascending aorta or arch has reached a high degree that it becomes evident on ordinary physical examination—inspection palpation percussion and auscultation. As a matter of

fact even roentgenology itself is a crude method of diagnosis deformity or calcification of the aorta being necessary before the roentgen ray picture appears abnormal. Frequently fluoroscopy shows greater dilatation of the aorta than is found at postmortem examination because of the dynamic dilatation present during life under high intra aortic pressure. Marked aortic

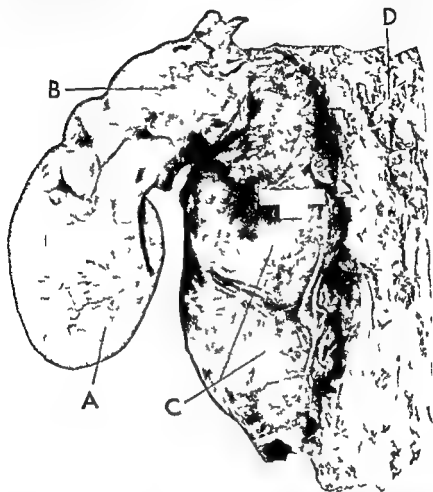


FIG 143 Syphilitic aorta with large aneurysm of the descending thoracic portion compressing and eroding the vertebrae and spinal cord with resulting paraplegia (A) Heart (B) arch of aorta (C) aneurysmal sac and (D) vertebral column (Kindness of Dr Pedro Castillo Havana Cuba)

pulsation is often visible fluoroscopically with marked aortic regurgitation especially when the heart action is very forceful. Occasionally large or thick aortic plaques (calcification) are apparent on roentgen ray examination. Finally it is important that roentgenologic examination should include the oblique views as well as the anteroposterior view because the shadow of the great vessels sometimes appears very wide in the anteroposterior view when



FIG 144 Roentgenograms showing a dense sclerotic aorta throughout its course in the thorax. The heart is slightly displaced to the right by the high level of the diaphragm on the left. The aortic notch in the barium filled esophagus is clearly visible at the beginning of the aortic arch. (A) Anteroposterior view (B) left anterior oblique view

the aorta is simply kinked or tortuous and not dilated. Erroneous diagnoses of dilatation and even of aneurysm have sometimes been made by hasty roentgen ray study. In obscure cases roentgen films taken after the intra venous or more usefully still arterial or direct aortic injection of contrast fluid may give the necessary information.

Dilatation of the aorta is usually accompanied by a systolic murmur more or less localized in the second intercostal space just to the right of the sternum varying in intensity and in extent of transmission but less intense and not so widely transmitted as is the systolic murmur of aortic stenosis. The most important points of differentiation between aortic dilatation and aortic stenosis are the obvious aortic enlargement by roentgen ray study in the former and the palpable systolic thrill, decrease or absence of the aortic second sound and decrease of pulse pressure often with plateau pulse in the latter. Lesser grades of aortic stenosis are difficult or impossible to diagnose especially if there happens to be coincident aortic dilatation. Dilatation of the aorta may be accompanied by signs of aortic regurgitation commonly organic and often due to syphilis but of functional nature in some cases. Marked rheumatic aortic regurgitation may result in aortic dilatation which is well shown by roentgen ray.

Enlargement of the left ventricle as evidenced by physical examination, roentgen ray study and electrocardiography (abnormal left axis deviation) follows aortic regurgitation complicating aortic disease while myocardial malnutrition, scattered fibrosis and even infarction may follow narrowing of the coronary mouths producing the usual signs such as abnormalities of the electrocardiogram already described (Chapter 21). Heart failure of congestive type may succeed either of the two complications of disease of the aorta which especially affect the heart, namely, aortic regurgitation and coronary mouth occlusion but especially the former. Slight to moderate degrees of acquired aortic disease usually produce no signs of cardiac involvement.

Signs due to aortic aneurysms will be discussed later in this chapter.

**Course and prognosis.** The course and prognosis of aortic disease depend on two conditions: the etiologic factor and the degree of involvement. Usually atherosclerosis is a slow process continuing to old age; it is not in itself a serious condition except in very rare instances of aortic wall rupture or of intra aortic thrombosis over an eroding or brittle plaque. Extensive atheroma is however an unfavorable omen for very long life since it exists more often in persons who die under the age of seventy five than in those who survive that age. Infectious aortitis may not be serious but it often is acute or subacute bacterial endarteritis like acute or subacute bacterial endocarditis with which it may be associated. It is now curable by the administration of penicillin or other specific remedy in the course of weeks or months while syphilitic aortitis which used to limit life to an average duration of about three years after its discovery now permits a good many long survivors when the newer measures of treatment are carried out (see Chapter 16). In the severer cases of rheumatic infection and typhoid fever aortic lesions may develop.

Rupture of the aorta as a rule is rapidly fatal but rare cases have existed in which the rupture was small or the bleeding gradual and even spontaneous repair has been noted

Aneurysms saccular or dissecting are serious the former permitting as a rule but a few months to a few years of life after their discovery and the latter generally fatal in the course of a few hours days or weeks infrequently a dissecting aneurysm allows survival for a few months or years with double aortic channel

**Complications** Important complications of disease of the aorta varying with the cause consist in the main of (1) cardiac enlargement and failure which may or may not be secondary to the aortic disease (2) aneurysmal formation and (3) rupture of the aortic wall The first and last of these complications have been discussed above aortic aneurysms will be discussed later in this chapter

Disturbance of the cardiac rhythm in aortic disease is unusual

**Treatment** The treatment of aortic disease varies with its cause and degree and with the type and extent of complications it is discussed separately under cardiovascular syphilis (Chapter 16) bacterial endocarditis (Chapter 15) congestive heart failure (Chapter 30) and aneurysm (the present chapter) There is no effective treatment as yet for atherosclerosis but avoidance of overexertion and overeating and protection against infection are advisable For a great many years potassium iodide has been given empirically in the treatment of arteriosclerosis there is a possibility but no real proof as yet, that this drug may have some influence in retarding the development of this process in man Choline and other lipotropic agents are now being tested in order to determine their therapeutic and prophylactic action in human atherosclerosis

**Differential diagnosis** The chief difficulty in the differential diagnosis of a diseased aorta comes in distinguishing it from a normal aorta since in a large majority of cases of atherosclerosis and inflammation there are no symptoms or signs and when there are such symptoms and signs they are often so slight or obscure that a clear diagnosis is impossible When aortic dilatation or other abnormalities are well marked they must be differentiated from mediastinal disease and tumors and from heart disease of other nature than that associated primarily with aortic disease Often the differentiation is difficult and in a large number of cases aortic disease is complicated by factors like hypertension coronary disease or valvular disease which obscure the primary aortic abnormalities

## CONGENITAL AORTIC DEFECTS

Congenital aortic anomalies found mostly in young persons are due to maldevelopment in fetal life or at birth and include hypoplasia coarctation right aortic arch double aortic arch vascular rings involving aorta—especially double aortic arch and major branches of aorta (in particular the right sub



clavian) and transposition of the aorta and pulmonary artery septal defects between aorta and pulmonary artery, right ventricle or atrium, and patency of the ductus arteriosus these defects are discussed in Chapter 13

### DISEASES OF THE PULMONARY ARTERY

The pulmonary artery is subject to nearly all the diseases and abnormalities that affect the aorta but in less frequency and degree. Nevertheless cases exist in which this artery and its branches are involved to a considerable extent and it has been shown in recent years that structural changes in the smaller pulmonary vessels are extremely common and sometimes play a role in the precipitation or exaggeration of circulatory trouble (Costa 1927 Brenner 1935).

An important new method of studying the pulmonary circulation with particular reference to its blood pressure has been introduced in the last few years and has already clarified some hitherto unsolved problems. This method consists in the catheterization of the pulmonary artery and its branches via the heart (see Chapter 10).

From a careful study of a series of 100 consecutive unselected autopsied cases at the Massachusetts General Hospital Brenner drew the following conclusions: This lengthy survey seems to show that the pulmonary circulation plays an important part both in the physiology and in the pathology of the circulation as a whole but that this part is with rare exceptions passive rather than active. The structure of the pulmonary vessels is such that they cannot be expected to play an important part in the regulation of the circulation through the lungs.

By far the most important influence in regulating the pulmonary circulation is the activity of the heart and particularly the state of balance between the two sides of the heart: an increased output of the right side or a diminished output of the left causing congestion of the lungs and vice versa.

Again the pulmonary circulation has so great a reserve (provided by the ready distensibility of the small pulmonary vessels and the large number of reserve capillaries through which blood does not ordinarily flow) that it is difficult to embarrass it by occluding large branches of the pulmonary artery. The cross sectioned area of the stem of the pulmonary artery must be diminished by 75 per cent before the systemic blood pressure falls and by 90 per cent before death occurs (in acute experiments).

Practically all the varieties of vascular disease occurring in the systemic circulation may be observed also in the pulmonary circulation. Some forms such as syphilitic arteritis are less common and others such as septic and tuberculous arteritis are more common than in the systemic circulation. Atherosclerosis is exceedingly common having been noted microscopically in some degree in 97 per cent of 100 consecutive unselected autopsies. Its incidence is therefore as great though its degree is not so marked as in the systemic circulation. Its very frequency makes it difficult to determine etiologic factors though its severity increases somewhat with age and with conditions

thought to be associated with a raised pulmonary arterial pressure such as cardiac disease or chronic pulmonary disease. No constant relationship is found between the thickness of the right ventricle and the degree of pulmonary atherosclerosis.

Thrombi whether embolic or formed *in situ* are common in the pulmonary circulation being found in 28 of 100 consecutive unselected autopsies. They ultimately become completely organized. They rarely cause symptoms unless a large branch of the pulmonary artery is suddenly blocked.

**Etiology and pathology.** The commonest lesion of the pulmonary artery wall is *atherosclerosis* which is found particularly in cases of chronic mitral valve disease and chronic lung disease (especially extensive fibrosis). Such atheroma has been attributed to the increased strain on the artery and its branches by the hypertension in the pulmonary circulation. In some cases pulmonary atherosclerosis exists without any lesion elsewhere. There is apparently but little relationship between sclerotic changes in the aorta and in the pulmonary artery. The pulmonary arterial atherosclerosis is usually slight consisting simply of yellowish fatty areas (atheroma) without calcification plaques which are so frequent in the aorta are unusual in the pulmonary artery. Atherosclerosis of this artery is thus of little or no significance in most cases it is simply a pathologic finding of academic interest.

*Infection of the pulmonary artery* is occasionally found in slight degree especially in rheumatic infection or bacterial endocarditis. Syphilitic involvement either of the main artery or of its smaller branches is very rare but it may be responsible for aneurysm or thrombosis of some part of the pulmonary arterial circulation.

*Endarteritis obliterans* of the smaller pulmonary arteries which is a rare but serious and generally rapidly fatal condition has been attributed in some cases to syphilis but as a rule it is of unknown cause.

*Congenital defects* include communications between pulmonary artery and aorta and transposition of these great vessels these have been discussed in Chapter 13. There is also hypoplasia associated at times with congenital pulmonary stenosis. Congenital dilatation is occasionally seen with patency of the ductus arteriosus with interatrial septal defects and even with pulmonary stenosis. Aneurysmal dilatation due to weakness of the wall may also occur but much more rarely.

*Trauma* is infrequent as a cause of pulmonary artery disease but rupture and traumatic aneurysm of the main trunk and of the branches have been noted as in gunshot wounds.

One of the most serious of all affections of the pulmonary circulation is that of obstruction by *thrombosis* or *embolism* most commonly the latter. Thrombosis is the result of a primary pulmonary artery lesion—endarteritis of inflammatory or obliterans nature—or perhaps of chronic stasis except when it occurs secondary to obstruction by embolism. Embolism is a sudden invasion of a generally normal pulmonary arterial tree by a clot from a thrombosed vein somewhere in the body (in the great majority of cases from legs

pelvis or abdomen)—this will be discussed in more detail in the next section of this chapter

*Hypertrophy of the smaller pulmonary arteries* with increased thickness of their walls is a common result of chronic pulmonary hypertension from any cause especially in younger patients

Finally *dilatation of the pulmonary artery* and its main branches without lesions of the wall except occasionally atheroma is a fairly common acquired finding with hypertension of the pulmonary circulation in mitral stenosis congenital atrial septal defects extensive blocking of the pulmonary circulation or advanced disease of the lungs Some of this dilatation is permanent but some is temporary due evidently to the dynamic effect of the increased blood pressure and acutely caused by massive pulmonary embolism before the circulation and the right ventricle fail Rarely pulmonary artery dilatation is congenital Regurgitation through the pulmonary valve may or may not be found in cases of pulmonary artery dilatation

The pathologic characteristics of the various lesions mentioned above are the same in nature but as a rule much less in degree than those described under aortic disease

**Symptoms** There are no symptoms of pulmonary artery disease itself except those associated with sudden occlusion of a large part of the pulmonary circulation by embolism with extensive obstruction of the smaller branches or with right heart failure In the case of massive pulmonary embolism there are at first usually air hunger and collapse and sometimes anterior chest oppression later fever cough hemoptysis and localized chest pain (due to infarction) usually develop if the patient survives the initial catastrophe With extensive obstruction of the smaller pulmonary vessels there are dyspnea and cyanosis When the right heart fails liver engorgement and dependent edema develop

**Signs** Signs of pulmonary artery disease are few In fact there are no signs at all unless there is dilatation of the main trunk and its major branches the presence of which may be shown by physical examination but much better by roentgen ray study or unless there is obstruction due to chronic endarteritis thrombosis or embolism when cyanosis and right heart failure may be marked The cyanosis due to the greatly limited area of pulmonary capillary surface exposed to the inspired air may be intense in rare cases especially in those with endarteritis to whom the term 'black cardiacs' has been applied Physical signs of pulmonary artery dilatation include a loud pulmonary systolic murmur accentuated pulmonary second sound increased percussion dullness at the left upper cardiac border and sometimes visible and palpable pulsation over the pulmonary artery A state of serious shock often fatal with very low arterial and venous blood pressures may supervene when there is sudden and considerable pulmonary obstruction due to embolism from peripheral venous thrombosis which occasionally occurs as a postoperative complication or even more commonly in the course of chronic heart disease

Frequently associated with abnormality of the pulmonary artery is right ventricular enlargement, revealed by various methods of study: there is left atrial enlargement only when the left ventricle has failed or mitral valve disease is present. With considerable dilation of the pulmonary artery the valve ring may become incompetent and the murmur of pulmonary regurgitation may then be evident.

Signs of infection underlying lesions of the pulmonary artery are of course incidental and do not aid materially in the diagnosis except in determining the type, as in the case of syphilis or acute bacterial endocarditis.

**Course and prognosis.** The course and prognosis of pulmonary artery lesions vary greatly. Usually they are entirely favorable but in the case of extensive pulmonary endarteritis obliterans the structural defect itself may prove fatal in the course of a few months or years. In the case of chronic stasis of high degree in the pulmonary circulation thrombosis and infarction may be superimposed on serious heart disease as an insupportable burden, and in the case of pulmonary embolism death may result in a few minutes, hours or days, or recovery follow after a more or less stormy illness. As a rule pulmonary artery disease is a postmortem finding, not diagnosed or diagnosable during life.

**Complications.** Complications consist chiefly in enlargement and failure of the right ventricle. There may or may not be other cardiovascular lesions present. Heart disease, especially mitral stenosis and left ventricular failure, are common. Pulmonary arterial aneurysms and rupture are very rare.

**Treatment.** The treatment is that of the underlying disease or complication. In the case of obstruction due to endarteritis, thrombosis or embolism, oxygen therapy should be employed to reduce cyanosis and dyspnea. Operative removal of pulmonary emboli has been successfully accomplished (first successful case reported by Kirschner in 1924) and frequently ad used in the past but only rarely has it been attempted, because it is excessively difficult to select the proper case and time for such a radical operation. It seems very unlikely from the experience of the last twenty years that such embolectomy will ever prove feasible. Preventive measures, however, have already proved their worth. If it is evident, for example, that pulmonary embolism has resulted from peripheral phlebothrombosis the leg veins should be ligated to prevent recurrence and for prophylaxis anticoagulant therapy is in order.

**Differential diagnosis.** The diagnosis of pulmonary artery disease is often impossible only with well-marked changes is it more than a guess. Differentiation from pulmonary valve lesions may be very difficult: the presence of mitral stenosis, of chronic failure of the left ventricle, of chronic pulmonary fibrosis, of recent operation or accident (which would favor pulmonary embolism) and of pulmonary artery dilation are the distinctive points which aid in the diagnosis of involvement of the pulmonary artery. Cardiac catheterization to determine the pulmonary arterial pressure is occasionally a helpful procedure. The differential diagnosis between pulmonary embolism and acute coronary occlusion is sometimes especially difficult, for this purpose serum

electrocardiography is of particular value (see Chapters 20 and 21 and the next section)

### PULMONARY EMBOLISM

In the first two editions of this book pulmonary embolism one of the most important of all cardiovascular disorders was seriously neglected but this omission was largely corrected by the addition in the third edition of ten pages about this subject In the present edition references to new advances have been added

It is an astonishing and disconcerting fact that I and many others had been examining and treating patients for years without realizing what we know now namely that pulmonary embolism instead of being predominantly a surgical or rather postoperative complication is actually much more commonly a condition occurring in the practice of internal medicine particularly in heart disease itself Until recently it has been called all sorts of things uncommonly recognized during life for what it actually was It has not suddenly appeared out of the blue a new disease in its frequency we have merely at last become aware of it

Its great importance lies not so much in its frequency but rather in its serious significance and in its preventability It belongs in some detail in this book not only because it is a cardiovascular event of much importance but because like dissection of the aortic wall it involves the great vessels and is an intrathoracic disease that may simulate or complicate heart disease itself in contrast to the various peripheral vascular lesions and especially because in its protean manifestations and details it is not adequately presented in most of the medical literature even of the present day

**Incidence** Pulmonary embolism is variously recorded as being found in 8 to 12 per cent of routine autopsies in 5 to 10 per cent of postoperative deaths in 0.1 to 0.5 per cent of all cases operated upon and sooner or later in a large percentage of cardiac patients (31 per cent of autopsied cases of mitral stenosis and 48 per cent of autopsied cases of congestive heart failure—Levine and White 1937 and Kinsey and White 1940 respectively) In one autopsy series 60 per cent of the cases were medical (half of which were cardiac) and 40 per cent were surgical (Hampton and Castleman 1940) of another series of 247 cases 166 were medical 80 postoperative or posttraumatic and one occurred postpartum (Westdahl 1941) In a recent survey of cases at the Massachusetts General Hospital there were 273 cases (0.6 per cent) among 45,523 medical patients and 238 cases (0.24 per cent) among 98,642 surgical patients during the years 1936 to 1945 inclusive (Carloti et al 1947) In my own cardiovascular practice the recognized incidence jumped from 0.4 per cent in the decade 1920 to 1930 up to 3.0 per cent in the decade 1930 to 1940 due in all probability to better acquaintance with the condition (White 1940) Even the pathologist and the roentgenologist with their accurate methods of study realize their large oversight of pulmonary em-

bolism in the past (Hampton and Castleman 1940) After World War I the German medical writers commented on the increased postwar frequency of pulmonary embolism (Burwinkel 1928) which was variously attributed to poor physical condition and malnutrition to the increase of surgery and because of the advance of surgery to the subjection of more older persons to operations though these factors were quite possibly operative it seems likely that the recognition of the condition was also keener Erdheim the great pathologist of Vienna had been one of the few who was early cognizant of the true situation

**Etiology Cause** The one outstanding cause of pulmonary embolism is *phlebothrombosis of the leg veins* beginning as a rule in the calf and extending into the long saphenous and femoral veins in one or both legs The thrombus is usually bland and dependent on stasis in a local circulation that has already been defective either structurally or functionally it is not infective or based on infection and so the term phlebothrombosis is preferable to thrombophlebitis Other veins in the body pelvic abdominal brachial and thoracic are much less likely to be responsible even though they may be at or near the site of operation or injury that has occasioned the rest in bed Nor are the right heart chambers often the locus of origin of the clots special exceptions should be made in the case of bacterial endocarditis involving a congenitally deformed right heart chamber or valve or patent ductus arteriosus and myocardial infarction of the interventricular septum with resulting thrombus formation on the injured myocardium

The leg phlebothrombosis occurs with equal readiness in the medical and in the surgical or traumatic cases predisposed by the circulatory stasis occurring in chronic or acute illness as from heart disease with congestive failure myocardial infarction cancer abdominal and pelvic operations and serious accidents Excessive manipulation of the abdominal or pelvic viscera at the time of operation and a long sustained Trendelenburg position favor the leg vein stasis Sitting still for hours with the knees bent favors the occurrence of thrombosis in the leg veins in an older person

**Exciting factors** In the majority of cases the embolus breaks loose without any particular provocation but sometimes some strain is responsible especially administration of an enema or use of a bedpan

**Age** Pulmonary embolism occurs postoperatively much more commonly in older persons but is fairly frequent as a complication of heart failure in middle aged or young adults it is rare before the age of twenty

**Sex** The sexes are fairly evenly represented

**Pathology** The structural changes concerned with pulmonary embolism are three (1) the clot in the leg vein which becomes the embolus (2) the actual plugging of one or more of the pulmonary arteries by that clot and (3) the pulmonary infarct that may follow Each one has its signs and symptoms The first two conditions always occur but not the third

**The clot itself** is a very rapidly propagating thrombus loosely attached to the wall of the leg vein and often floating in the blood stream ready to break loose

at any moment. If in the course of its evolution this clot becomes well fixed it then loses its threat and in time becomes organized in situ doubtless that frequently happens and we never know how often patients escape further trouble. By the time a clot becomes solid and by obstructing a vein produces signs and symptoms that particular clot has lost its embolic tendency although a sister or daughter clot may still get loose. Thus in phlebothrombosis the pulmonary embolus may come from the leg that seems normal the other leg being swollen and sore as the result of the venous obstruction which has revealed the underlying disease. It is the lengthy clot from the long saphenous or femoral vein that is especially dangerous and that coiled up may massively block the main pulmonary artery.

The actual *blockade of blood flow* in the pulmonary circulation varies tremendously in degree and location from almost complete obstruction of the main pulmonary artery to closure of a small branch on either side the former kills quickly the latter in an otherwise healthy person probably produces no symptoms or signs at all. Rarely is the embolus a septic one or composed of tumor cells or in the dog made up of the long worms of *Dirofilaria immitis*. The left lower lobe has been the most common location of embolism or infarction at the Massachusetts General Hospital but both lower lobes are frequently involved together during the years 1937 to 1943 the location of 171 pulmonary emboli at the Massachusetts General Hospital has been as follows: left lower lobe 99 (57.9 per cent) right lower lobe 65 (38.0 per cent) right upper lobe 4 (2.3 per cent) right middle lobe 0 and left upper lobe 3 (1.8 per cent). Pulmonary embolism is often perhaps usually multiple sometimes as many as one to two dozen emboli enter the lungs in the course of a few days or weeks varying in size from small fragments of clot to thrombi a foot or more long which may cause rapid death.

*Pulmonary infarction* is by no means a necessary sequel of pulmonary embolism being found in only about half of the recognized cases of pulmonary embolism. The pulmonary circulation is so rich in anastomotic and collateral connections that infarction results only if the occlusion is large or the apex of one of the lobes is involved or some obstruction to the blood flow is already present as in congestive failure of the left ventricle or in mitral stenosis. The infarction may be partial and temporary yielding no signs and leaving no scar or it may be complete with ample signs and scar formation. Thus it is obviously important not to use the terms pulmonary embolism and pulmonary infarction synonymously.

**Symptoms.** The symptoms of pulmonary embolism vary from none to many, from mild to overwhelming. The commonest is the sudden onset of *dyspnea* not attributable to effort or excitement or to abrupt heart failure from paroxysmal tachycardia in a cardiac patient. Rarely an asthmatic type of breathing is set off. A symptom that is a close second is *substernal oppressive pain* which often accompanies the dyspnea and in older patients with limited coronary reserve may include or actually consist entirely of angina pectoris due to the effect of anoxemia or of the strain of the event on coronary heart

disease already present on occasion the pain may predominate. A *feeling of faintness* is common while a *state of shock* is not at all rare being found naturally in the more severe cases or in patients already quite ill before the pulmonary embolism occurs. *Restlessness* and *sweating* are often seen as a part of the reaction to the embolism. Other symptoms are uncommon: nausea and vomiting, cough, chill and headache. Sometimes a mere sense of uneasiness or malaise reveals the occurrence of a small embolus.

*Fever* develops if there is an infarct in the lung but there may already be a slight febrile reaction to the underlying phlebothrombosis in the leg. With a large infarct the temperature may rise to 103° or 104° F by mouth. Fever of a degree or two that occasionally accompanies congestive failure is more often due to pulmonary infarction than to any other cause: it has been in the past wrongly ascribed to pulmonary infection which may to be sure occur (but less commonly) or to the congestive heart failure itself.

*Pleural pain* on the affected side is a common complication if there is an infarct, becoming evident on respiration on the second day and continuing for a few days with or without a pleural friction rub.

*Blood spitting* is important evidence in favor of the diagnosis if it occurs but it is actually relatively uncommon. It is often in larger amounts than in the case of pneumonia and does not resemble the frothy pink sputum of the pulmonary edema of acute left ventricular failure. Most cases of congestive heart failure do not raise any blood at all.

**Signs.** The two most important signs of the acute process and for a while afterward are *cyanosis* and *tachycardia* out of all proportion to any evidence of heart failure, pneumonia or fever. The cyanosis is frequently of high degree and is the occasion for rushing oxygen to the patient. The tachycardia on occasion is of paroxysmal nature: atrial ectopic or atrial fibrillation or atrial flutter and this abnormal rhythm may divert one's attention from the underlying lesion. As a rule however the tachycardia often as fast as 140 to 160 is sinus in origin: the patient may himself become aware of the fast pulse but usually he is more troubled by other things particularly the dyspnea and prostration.

*Jaundice* is a rare but important sign of a large pulmonary infarct superimposed on a liver congested from heart failure and unable to cope with the excess of blood pigment.

**Localizing signs** either of the *phlebothrombosis in the leg* (tenderness, swelling, pain on flexion of the foot—Homan's sign) or of the *involvement of the lung* (local rales, bronchial breathing, pleural friction rub or fluid) are often conspicuous by their absence. They should be looked for daily when found they aid greatly in the diagnosis.

**Laboratory data.** Information derived from laboratory study is usually less important than the symptoms and signs already presented: sometimes it is helpful in confirming or even pointing to the correct diagnosis but at other times it is misleading because it shows so little or because it reveals unexpected findings.



*Roentgen ray examination* At the onset and for 24 hours or more afterward there may be little to find wrong in the thorax by roentgen ray even with developing infarction of the lung except for elevation of the diaphragm on the affected side or distended main pulmonary trunks with decreased caliber of vessels below helpful signs which should be looked for. If there is no infarction roentgen ray evidence may be lacking but sizable infarcts finally appear in the picture as shadows of any shape and size at the periphery of either lung often tucked away in the sharp costophrenic angles where they may be mistaken for fluid. Besides the two difficulties with roentgen ray diagnosis of pulmonary embolism already mentioned namely the slow development of the evidence when such finally appears and its complete absence when there are no infarcts there is one other problem that is often insuperable namely that the shadow of an infarct may be hidden by the hydrothorax or pulmonary congestion due to underlying heart failure by pleural fluid resulting from the infarct itself or by the heart shadow which is so often enlarged in these cases.

Multiple shadows may appear in the lungs on the roentgen ray films due to recurrent emboli with infarcts and be mistaken for areas of bronchopneumonia or tumors (Figure 145A) and in recent years linear scars of pulmonary infarcts have been identified by pathologist and roentgenologist (Hampton and Castleman 1940) so that it is possible on occasion to unravel past episodes of pulmonary embolism (Figure 145B). Indeed sometimes old scars and fresh infarcts are present in the same case.

In pulmonary embolism it is even more important to investigate the venous circulation in the leg than it is to study the lungs inasmuch as the threat to further trouble which may be fatal lies in the femoral veins. Physical examination may quickly reveal the thrombosis by the discovery of tenderness, swelling or recently discolored skin and then roentgen rays are unnecessary but often (in over 50 per cent of the cases) there are no signs of the thrombosis. One may of course assume that it exists none the less and go ahead with the ligation of the leg veins on both sides without more ado. Some years ago it was the custom in various clinics for roentgenologic diagnostic purposes to inject some contrast medium (e.g. Diodrast) into the veins of the lower leg when thrombosis therein was suspected but this procedure has been in large part abandoned for two reasons (1) the veins even though not thrombosed were not always adequately filled and (2) on occasion thrombosis was actually precipitated or aggravated by the material injected.

*Electrocardiography* In the majority of cases of pulmonary embolism the electrocardiogram is of no assistance. A few cases about 10 per cent with severe enough pulmonary arterial obstruction to cause the acute cor pulmonale but without severe shock have electrocardiograms with characteristic pattern of dilatation of the right ventricle consisting of prominence of S waves in Lead 1 and in the precordial leads over the left ventricle of Q waves in Lead 3 low to slightly inverted T waves in Lead 2 inverted T waves in Lead 3 and in the precordial leads over the right ventricle (Leads V<sub>1</sub>, V<sub>2</sub> and sometimes V<sub>4</sub>) (McGinn and White 1935 Murnaghan McGinn and White 1943) (See Figure 99 and Chapter 20)



FIG 145 Roentgenograms showing (A) fresh pulmonary infarcts of lower lobe of right lung (kindness of Dr Richard Schatzki Mt Auburn Hospital Cambridge) and (B) clearing infarct upper portion of right lower lobe (kindness of Dr M C Sosman Peter Bent Brigham Hospital Boston) (C) (a) 12 days before and (b) one day after the occurrence of postoperative pulmonary embolism. Note in *b* the thrombosed pulmonary arteries consisting of rounded shadows at the hilus regions in contrast to *a* and the decreased vascular markings below the hilus shadow on the right resulting from the decreased blood flow there.

Besides the relatively small number of cases of pulmonary embolism showing the acute cor pulmonale pattern of electrocardiogram there are three other groups the largest of which because either of the small size of the embolus or at least of its failure to disturb the heart appreciably shows no change in the record from the normal or abnormal findings prior to the embolism. Another fair sized group consisting of older persons with limited coronary reserve and often already afflicted by coronary heart disease may develop under the strain of the pulmonary embolism itself or of the vascular shock that accompanies it sufficient myocardial ischemia and anoxemia to produce coronary types of electrocardiograms (see Chapter 21), or indeed even acute myocardial infarction itself (posterior or anterior) without actual acute coronary thrombosis. Finally severe depression of the coronary circulation with anoxemia in high degrees of pulmonary artery obstruction or vascular shock may itself cause temporary changes in the electrocardiogram which may simulate coronary heart disease though none has been present previously or will result after recovery.

Thus it is apparent that the electrocardiographic findings in pulmonary embolism can be entirely normal quite characteristic of one pattern or another or very complicated due to a combination of several effects (Murnaghan McGinn and White 1943).

**Other data** Other laboratory findings in pulmonary embolism are unimportant. Leukocytosis of slight to moderate (rarely high) degree is found when there is pulmonary infarction which explains the blood picture as it does the fever in many cases of congestive heart failure. Examination of blood sputum, urine and chest fluid shows nothing of special interest.

**Course and prognosis** Pulmonary embolism may kill quickly though not instantaneously but more often there is recovery. Of one group of 70 fatal cases 6 died in less than ten minutes and 16 more within an hour of the remaining 48 cases 20 died within twelve hours 4 between twelve and twenty four hours and 24 lived for one to several days (de Takats 1940). Of the cases that recover many have recurrent embolism in de Takats series of 100 cases 39 per cent suffered a second attack 12 per cent had a third 5 per cent a fourth 3 per cent a fifth and 1 per cent a sixth. Doubtless the embolism is often so slight that it escapes notice altogether.

This common recurrence of pulmonary embolism is one of its chief diagnostic features setting it apart from the two conditions with which it is so often clinically confused namely, myocardial infarction and pneumonia which do not so rapidly recur daily or weekly. Perhaps a patient does have acute coronary occlusion or pneumonia to start with but when some sort of acute trouble in the chest keeps repeating itself every few days one should not only think at once of pulmonary embolism but also suspect that even the first attack of all may have been that very condition.

Pulmonary embolism may occur as early as the first day after operation or accident or it may not happen till after three months in a large series of cases (897) at the Mayo Clinic approximately one half occurred between the

seventh and fourteenth days one quarter during the first seven days and one quarter after the fourteenth day (Barker et al 1941) The intervals between first and second episodes or between first and last (if more than two) in 207 cases of recurrent embolism in the Mayo Clinic Series was less than a day in 27 per cent between 1 and 7 days in 38 per cent more and less than 10 days in about four fifths of the cases In recurrent embolism the attacks vary greatly in severity from very mild to fatal thus the symptoms and signs will vary accordingly If the first attack or two have been severe however a succeeding slight attack may be enough to kill the patient or at least to cause symptoms and signs out of all proportion to the actual size of the embolus Likewise if serious heart or other disease is already present the very first pulmonary embolus even though small may precipitate congestive failure or myocardial infarction or be the cause of death in fact the commonest last straw which terminates life in patients with heart disease is pulmonary embolism

The mortality from recognized pulmonary embolism is variously estimated as 20 to 40 per cent but doubtless this figure is too high small emboli remaining undiagnosed Nevertheless it remains one of the most fatal of diseases

Recovered cases of pulmonary embolism may show no sequelae whatsoever or they may bear the linear scars of the pulmonary infarcts identified by roentgen ray and autopsy Such scars are as a rule entirely unimportant Rare cases however of massive pulmonary embolism recover to develop slowly the chronic cor pulmonale (doubtless having suffered originally from the acute cor pulmonale) The large clot in the pulmonary artery or its main branches becomes organized and the marked pulmonary hypertension gradually enlarges the right ventricle so that in the course of a few months or years death may come with right heart failure with or without recurrent pulmonary embolism from recurrent phlebothrombosis or pulmonary thrombosis in situ superimposed on the old organized embolus

**Complications** The commonest complication of pulmonary embolism is pulmonary infarction already described Attending such infarction there may be pleuritis and pleural effusion or a secondary infection of bronchopneumonia Acute vascular shock is an occasional and very serious complication Another reaction which has been described is that of bronchial and perhaps coronary spasm secondary to the vagal reflex set off by the event the frequency degree and importance of this have not been demonstrated In a minority of cases probably about 10 per cent there is an important degree of dilatation of the right ventricle (the acute cor pulmonale—see Chapter 20) In the presence of heart disease the serious complications of congestive heart failure and myocardial infarction may be further complicated by pulmonary embolism which vice versa, in its turn may precipitate either congestive failure or myocardial infarction

**Treatment** The lesser degrees of pulmonary embolism may require no treatment per se but cases of severe grade with dyspnea oppressive pain cyanosis and tachycardia with or without the acute cor pulmonale or shock need emer

agency treatment consisting of opiate (e.g., morphine sulphate  $\frac{1}{4}$  gr [0.015 gm] subcutaneously), oxygen (by tent or Boothby mask in high concentration preferably 100 per cent) and expert nursing care. The first few hours are the critical ones.

Other therapy is less important but may be helpful. Atropine sulphate  $\frac{1}{100}$  to  $\frac{1}{60}$  gr (0.0006 to 0.001 gm) and also papaverine hydrochloride  $\frac{1}{2}$  gr (0.03 gm) have been advised subcutaneously or even intravenously for rapid effect in the syncopal type of pulmonary embolism as antispasmodics but their routine general value has not been proved. Also digitalis solution (equivalent to 0.3 gm or  $4\frac{1}{2}$  gr of the international standard strength) or strophanthin ( $\frac{1}{100}$  gr or  $\frac{1}{2}$  mg) has been advised to be given intravenously for the acute cor pulmonale but the effectiveness of these drugs also remains to be demonstrated.

Otherwise only symptomatic treatment is indicated except for two important measures. If the diagnosis is clear either the leg veins should be ligated at once or the anticoagulant heparin be given by vein or Dicumarol begun by mouth to maintain a clotting time of  $\frac{1}{2}$  to 1 hour. The leg veins should be investigated the offending veins (commonly the superficial femorals) being ligated preferably on both sides to prevent further embolism which might well be fatal. At the time of ligation it may be possible to remove the thrombus from the vein by suction. Anticoagulant therapy alone may not be adequate in the face of thrombi already formed if pulmonary embolism occurs or recurs during its use vein ligation should be done at once. Even this ligation however may not be a panacea although it is usually effective patients have been observed in whom a dangerous thrombosis above the site of the ligatures has followed the operation. In rare cases it has been found necessary to ligate the inferior vena cava.

Pulmonary embolectomy first carried out nearly two decades ago (1924) has not proved to be feasible at least as a routine measure. Although it may conceivably be actually lifesaving in rare cases it is a radical procedure which may readily tip the delicate balance of the scales the wrong way it is not a simple operation in itself, it may not reach the offending emboli which may be out of reach in both lungs and in the majority of cases of pulmonary embolism recovery occurs without it.

*Prevention of the leg phlebothrombosis* that gives rise to pulmonary embolism is more important than its treatment. In the first place a state of physical and especially circulatory fitness should be established and maintained so far as possible especially prior to surgical operation. At the time of operation as little as possible should be done especially in older persons and positions on the operating table conducive to blocking of the pelvic and leg veins should be avoided so far as possible. Postoperatively and in any prolonged illness as from heart failure the leg circulation should be fostered by massage passive and active exercise and getting the patient out of bed at the earliest possible moment. The routine postoperative use of the anticoagulants heparin and Dicumarol is open to question cases very prone to phlebothrombosis however should be so treated.

**Differential diagnosis** The four conditions with which pulmonary embolism is most commonly confused are pneumonia congestive heart failure acute myocardial infarction and paroxysmal tachycardia The differentiation is usually easy by history and physical examination alone but now and again roentgen ray evidence or the acute cor pulmonale electrocardiogram or the course of the illness with recurrent attacks solves the problem The hardest cases are those in which two or even three of these conditions are superimposed in such patients careful detective work is necessary The most important clues pointing toward pulmonary embolism are leg phlebothrombosis recent operation or injury very abrupt onset unusual degree of cyanosis blood spitting of moment unusually fast pulse and respiratory rates in the presence of relatively slight fever and recurrence of attacks

### COMMUNICATIONS BETWEEN THE AORTA AND THE PULMONARY ARTERY

There are four types of congenital communication between the aorta on the one hand and pulmonary artery right ventricle or right atrium on the other hand They are first and most common patency of the ductus arteriosus second rare cases of a persistent truncus arteriosus without separation into aorta and pulmonary artery third exceptional instances of communication between the aorta and pulmonary artery by arterial septal defect and fourth very rare cases of communication between aorta and right ventricle or right atrium by septal defects (see Chapter 13) In differential diagnosis a possible rupture of the aorta into right ventricle or right atrium in bacterial endocarditis and endarteritis has already been mentioned (see Chapter 15) and rupture of aortic aneurysm into pulmonary artery or heart chamber will be discussed below

### ANEURYSMS

Vascular aneurysms (*αιμαρισμα* a widening) are most commonly arterial infrequently arteriovenous Cardiac aneurysms so-called have been described in Chapter 25

### SACULAR ARTERIAL ANEURYSMS

Arterial aneurysms are not uncommon structural defects unimportant when small or involving a peripheral artery but often serious always a potential source of trouble through rupture and even subject to infection (bacterial endarteritis) Their incidence varies widely since it depends in large part on the incidence of syphilis and trauma in any community and doubtless also on their early recognition and satisfactory treatment Although partly because of earlier recognition and more satisfactory treatment of these conditions in the last two decades it is mostly because of prevention that aneurysms are definitely less common in some places than they were a generation or two ago

In a series of 600 postmortem examinations at the Massachusetts General Hospital in the years 1896 to 1900 there were six individuals (1 per cent)

who had syphilitic aneurysms four of the aorta and two of the innominate artery while in three more recent series of 600 autopsies each at the same institution in the years 1926 to 1930 1936 to 1938 and in 1950 there were three cases (0.5 per cent), two cases (0.3 per cent) and one case (0.16 per cent) respectively with syphilitic aneurysms five of the aorta and one of the innominate artery. Mycotic and dissecting arteriosclerotic aneurysms are not included in these figures. Altogether there were 54 aortic and 3 innominate syphilitic aneurysms in the first 5,600 autopsies at the Massachusetts General Hospital in a period of 33 years (just prior to 1930). There were in this same series 10 dissecting aneurysms of the aorta and a few mycotic aneurysms figures of which it is difficult to be certain about since they have been carefully looked for only in recent years.

The diagnosis of syphilitic aneurysms was made clinically at the Massachusetts General Hospital in 113 of 51,875 patients (0.2 per cent) during the decade from 1900 to 1910 and in only 61 of 75,184 cases (0.08 per cent) during the decade from 1925 to 1935 despite the improved roentgenologic facilities for diagnosis. These percentages show a marked reduction in recent years and are probably significant of a decreasing incidence of aortic syphilis in New England as evidenced also by a decreasing incidence of syphilitic aortic regurgitation.

In a series of 12,000 postmortem examinations in Philadelphia 306 intracorporeal arterial aneurysms of all kinds were found in 268 patients (2.1 per cent) (Lucke and Rea 1921).

**Etiology Cause** Syphilis is the most common cause of arterial aneurysms of the aorta and other great vessels of the trunk about 90 per cent of such aneurysms being produced by this infection. Arteriosclerosis has relatively recently become recognized as the next most frequent cause of aortic aneurysms especially in the abdomen though in the thorax arteriosclerotic aneurysms are rare (Ruffin, Castleman and White 1941). Trauma is the commonest cause of arterial aneurysms in the extremities with the infections of bacterial endarteritis and rheumatic fever and congenital weakness of the arterial wall acting as infrequent factors.

**Age** Because of the great preponderance of syphilis as a cause large arterial aneurysms are generally found in middle aged persons forty to fifty five years old. However syphilitic aortic aneurysms may be found quite frequently in younger individuals also, especially in Negroes even before the age of thirty years and rarely in children with congenital syphilis. Traumatic and non-syphilitic infectious aneurysms may occur at any age but are most frequent in youth.

**Sex** There is a great male preponderance in the incidence of aneurysm because of the far greater frequency in the male sex of the two chief causes syphilis and trauma. The ratio of male to female incidence is about 10 to 1.

**Race** Aneurysms are found 6 to 8 times more often in Negroes than in white people, not only because of the greater incidence of syphilis in Negroes

but probably also because of its less satisfactory treatment among them and particularly perhaps because of the heavy type of Negro labor

**Pathology** An arterial aneurysm consists of a marked dilatation of an artery local or general saccular or diffuse it ordinarily signifies a local bulging of the wall to form a sac The larger arteries are more often the site of aneurysms than are the smaller arteries because they are more often the seat of an infection which weakens the wall especially syphilitic mesaortitis and because they are under greater strain Of the larger arteries the aorta is most often involved and the ascending portion of the aorta more frequently than any other part because it is the usual location of syphilitic aortitis The relative frequency of aneurysms of various arteries was found to be as follows in two series of 530 cases (Crisp 1847) and 1 000 cases (Klotz 1926) respectively

Table 13

## LOCATION OF ARTERIAL ANEURYSMS

	<i>Crisp</i>	<i>Klotz</i>
Thoracic aorta	175	610
Popliteal artery	137	
Femoral artery	66	
Abdominal aorta	59	108
Carotid artery	75	
Innominate artery	70	
Subclavian artery	23	
Axillary artery	18	
External iliac artery	9	
Cerebral artery	7	
Common iliac artery	2	
Posterior tibial artery	2	
Gluteal artery	2	
Pulmonary artery		
Brachial artery	1	
Subscapular artery	1	
Ophthalmic artery	1	
Temporal artery	1	
In the brain		133
In regions other than brain and aorta		0*

In 23 of these cases the \* were aortic aneurysms in both thorax and abdomen

The relative frequency of sites of aortic aneurysms is about as follows on a basis of 10 for aneurysm of the ascending aorta ascending aorta 10 aortic arch 7 descending thoracic aorta 3 abdominal aorta 3 The chief sites of aneurysms other than in the aorta are the popliteal femoral carotid subclavian innominate axillary and iliac arteries and the chief sites of visceral aneurysms are the splenic and hepatic arteries

As noted above the chief cause of peripheral aneurysms in arms and legs is traumatic with bulging of the wall at the site of stab or gunshot wound or of crushing injury there having occurred a partial healing of the original lesion The chief cause of *cerebral aneurysms* is a congenital defect of the



wall of the circle of Willis at a junction of the vascular ring with one of the incoming branches in the course of years amounting to 30 or 40 or more the thin wall bulges at this point to form an aneurysm of about the size of a pea it is the rupture of this aneurysm in certain of the cases that gives rise to the important not very rare *subarachnoid hemorrhage* which abruptly indicates its presence by headache blood in the spinal fluid and sometimes syncope and death though recovery not infrequently occurs Although syphilitic *mesaortitis* (see Chapter 16) is the commonest cause by far of thoracic aortic aneurysms *arteriosclerosis* is a common cause of *abdominal aortic aneurysms* and may even account for an occasional thoracic aneurysm An interesting variant is the *senile ectasia of the ascending aorta* due to loss of elasticity and occasionally noted in old men or women without syphilis rarely does it reach the size of large syphilitic aneurysmal dilatation Ruffin Castleman and White (1941) analyzed 9 600 autopsy records of the Massachusetts General Hospital and found 60 syphilitic aneurysms of the thoracic aorta and only 3 syphilitic aneurysms of the abdominal aorta in contrast to 27 arteriosclerotic aneurysms of the abdominal aorta and only 3 arteriosclerotic aneurysms of the thoracic aorta in this same series there were 3 cases of well marked senile ectasia of the thoracic aorta On the other hand Scott (1944) reported that of 62 cases with aneurysms of the abdominal aorta 74 per cent were syphilitic 21 per cent arteriosclerotic and 5 per cent mycotic

A weakening of the arterial wall chiefly through the destruction or break of the muscular and elastic tissue causes a local or general stretching which in turn results in dilatation (Figure 143, page 748) If the process is gradual enormous outpocketings may occur so that saccular aortic aneurysms may develop of the size of the heart itself or even of a person's head Usually death from rupture heart failure angina pectoris or other complication takes place before an aneurysm can become very large especially if the process is rapid or the wall very weak The aneurysmal lining may be smooth or wrinkled atheromatous or ulcerated and the sac may be so filled with thrombus that it pulsates little or not at all Organization of the thrombus with little or no progression of the syphilitic process may follow a virtual repair of the aneurysm

A bacterial infection of the arterial wall usually a complication of subacute bacterial endocarditis, may result in a so called *mycotic aneurysm* When a lesion actually destroys the arterial coats it differs from the usual aneurysmal dilatation of an artery and so is then called a *false aneurysm*

*Rupture* of an aneurysm may occur anywhere an aortic aneurysm ruptures usually into the pericardial sac or a pleural cavity but sometimes into the mediastinum esophagus trachea great veins pulmonary artery, or atria and sometimes even externally through the skin

Dissecting aneurysms will be considered later in this chapter as a special type

*The effect of aneurysms on the heart and other structures* The heart itself is but little or not at all involved by an arterial aneurysm even by a large aortic

aneurysm unless aortic valve or coronary artery mouths are affected but secondary effects on various tissues or organs in the neighborhood of an aneurysm due to pressure are common such effects include erosion of sternum ribs and vertebrae obstruction and displacement of pulmonary artery esophagus and trachea collapse of a lobe of the lung and irritation or destruction of contiguous nerves causing pain or paralysis as in the case of pupillary and laryngeal abnormalities

**Symptoms** There are no symptoms of aneurysms themselves except as they cause pressure on surrounding structures (giving rise to dyspnea dysphagia cough hoarseness and pain) or affect the heart by their complications (giving rise to congestive failure or angina pectoris) It is of considerable interest to know that even large aneurysms may be symptomless the slow stretching and erosion of the arterial wall itself not ordinarily causing pain

**Signs** Signs of aneurysms are frequent but not always clear without complete examination the condition may remain undiscovered Signs are due in the first place to the vessel enlargement itself which may be seen or felt or if in the deeper part of the thorax observed by roentgen ray examination The anterior thoracic wall front of the neck popliteal spaces thighs and axillae are frequently the sites of the pulsating tumors caused by aneurysms bulging the skin and subcutaneous tissues out beyond their normal level Such aneurysmal swellings may be found even in the back at the left costal margin or in other unusual locations If an aneurysm is abdominal intracranial or deeply seated in the extremities it may be impalpable and invisible even to the roentgen ray No reliance can be placed on pulsation systolic murmurs and palpable systolic thrills over aneurysms they may or may not be present dependent on the depth of the aneurysm below the surface of the body the elasticity of the wall the size of the lumen and the presence or absence of thrombosis Aside from evidence of arterial enlargement itself there are frequent signs due to pressure on surrounding structures such as are produced by any tumor mass Arterial pulsation distal to an aneurysm is often delayed and decreased due not so much to the presence of the aneurysm as to a greater or lesser degree of occlusion of the arterial mouth which may be in the aneurysm The radial pulses are frequently unequal in cases of aneurysm of the thoracic aorta and sometimes one pulse or rarely even both pulses may be absent adequate circulation being maintained in the arms by collateral blood supply Very rarely clubbing of the fingers may result from inadequacy of the circulation in one hand or in both hands due to the effect of an aortic aneurysm In aneurysms of the thoracic aorta the Wassermann reaction is usually positive it was found to be positive in 50 cases (82 per cent) among 61 Negroes with thoracic aortic aneurysms (Sanford 1931)

The most reliable evidence of aneurysms of the thoracic aorta is to be obtained by roentgen ray study especially of those involving the arch or descending aorta a pulsating bulge of the aorta itself is the roentgen ray evidence (Figure 146 page 770) Both the new electrokymography (see Chapter 8) and roentgen ray study of the contours of heart chambers and great vessels out

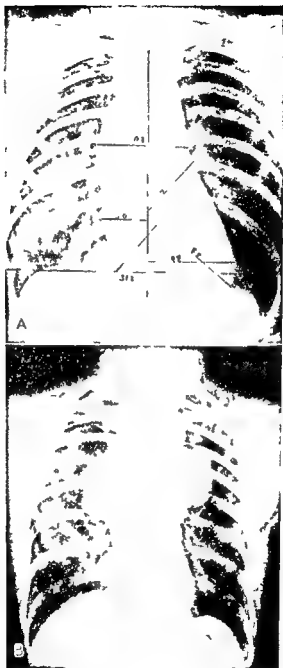


FIG 146 Roentgenograms showing aortic aneurysms (A) Small aneurysmal bulge of the ascending aorta due to syphilitic aortitis with poorly defined aortic knob and normal heart size (B) Multiple aneurysms of the thoracic aorta with normal heart size

lined by Diodrast injected into vein or artery can be very helpful in doubtful cases but careful technic and rich experience are usually needed to get the best results. Electrocardiography is of no value in the diagnosis of aneurysms.

On occasion in the absence of roentgen ray examination the very first evidence of an aortic aneurysm has been its rupture with fatal hematemesis for example.

**Course and prognosis.** A small traumatic aneurysm may not in any way limit activity or duration of life but a large aneurysm of a large artery especially since it is commonly syphilitic generally causes death in a few months to a few years and is associated with very serious disease. The usual aortic aneurysm has an unfavorable prognosis but occasional cases are encountered in which such an aneurysm may remain more or less latent without change for 5 to 15 years with or without special treatment. The most important point often overlooked concerning the prognosis and result of treatment of an aneurysm especially one of the thoracic aorta is that hard physical work has an unfavorable effect on the course of life. The more strenuous the activity the shorter the life and the poorer the result of therapy.

Rupture of an aortic aneurysm is not always fatal. Small leaks may heal and even perforation into the pulmonary artery is compatible with months to a year or more of life (Porter 1941; White, Chamberlain and Kelson 1941).

**Complications.** The chief complications of aneurysms already mentioned are those due to secondary cardiac involvement, pressure effects on surrounding structures, and rupture.

**Treatment.** The treatment of aneurysms is of three kinds: (1) that of the cause, (2) that of the complications, and (3) that of the aneurysm itself. If syphilis is the cause (as it often is) and there is no heart failure, specific therapy should be instituted with care as outlined in Chapter 16.

In earlier editions of this book the reader was warned that the progress of this treatment must be followed in great detail and the heavy metals discontinued if symptoms of cardiac failure appear or if the aneurysm increases rapidly in size apparently as the result of the rapid resolution of the lesion by the drugs but the introduction of penicillin in the treatment of syphilitic aortitis renders much of this old advice now obsolete.

Serious complications of heart failure and angina pectoris are to be treated as outlined in Chapters 21 and 30 of this book. Pain due to pressure on and erosion of surrounding structures may be relieved temporarily by morphine but paravertebral alcohol injection or sympathectomy which affords more permanent relief is much to be preferred.

In some cases where an aneurysm is saccular or easily accessible surgery may be indicated. For a peripheral aneurysm obliteration of the sac has been done by rapid or gradual ligation of the artery in one or several operations, the speed of arterial occlusion which may be extended over weeks or months depending on the extent of collateral circulation to the part of the body supplied by the artery involved. A second procedure has been the wiring with or without electrolysis of saccular aneurysms of larger arteries like the aorta,

here a coil of platinum gold or silver wire is inserted into the aneurysmal sac preferably under roentgen ray control. The presence of this wire and the passage through it of a small electric current may result in thrombosis in the aneurysmal sac tending to retard further progress of the lesion and to relieve distress such thrombosis however is by no means a constant result of this procedure. The third surgical maneuver is to support the affected vessel or sac by surrounding it with strong connective tissue for example a sheet of fascia lata or with cellophane. In August 1949, Abbott reported having applied cellophane to thoracic aneurysms in 32 instances with internal wiring in addition in four of these patients. The majority of the lesions were syphilitic in origin. On two occasions the procedure was carried out even in the presence of active massive hemoptysis. All of these methods have been employed but the first is most often applicable and is the method of choice for peripheral aneurysms. Care must be used to ascertain the presence of a sufficient collateral circulation before the artery in question is occluded. The accompanying vein should be ligated with the artery.

**Differential diagnosis** An arterial aneurysm is usually easy to diagnose except when it is deep-seated but when thrombosed it is sometimes very hard to differentiate from a tumor of other nature especially if that tumor is vascular and pulsating. The close structural relationship to some artery the marked pulsation often present and the history of trauma or history or proof of syphilis are the most important findings favoring a diagnosis of aneurysm. All methods of study must be used in doubtful cases especially in patients with thoracic and abdominal aneurysms.

### DISSECTING ANEURYSMS

Dissecting aneurysms must like arteriovenous aneurysms be considered by themselves for they form a distinct though small clinical and structural pathologic group (Shennan 1934). They involve chiefly the aorta occasionally the first part of the aortic branches due to extension from the aorta and rarely other vessels such as the coronary arteries independently.

Until the last decade dissecting aortic aneurysms were merely postmortem surprises but now they are frequently recognized clinically as evidenced by the steady accumulation of reports of correct antemortem diagnoses.

**Etiology Cause** The essential cause of dissecting aneurysms is a weakness in the media in the case of the aorta a medial necrosis of unknown cause (Erdheim 1929). A second factor usually of great importance is hypertension. A third factor infrequently is atherosclerotic disease of the arterial wall. Syphilis is only very rarely a contributing cause apparently in only 2 of 64 cases reported by Mote and Carr in the year 1942. Strain or even trauma may be rarely a precipitating factor (Leonard 1945).

**Age** Dissecting aneurysms are found most commonly in middle aged and elderly subjects rarely before the age of 30 years. A very young case of dis-

secting aneurysm of the aorta has been reported within the last few years in a boy 15 (McLaurin 1945)

**Sex** The male sex is predominantly affected in the ratio of about 3 to 1

**Pathology** The dissection apparently begins in the media as the result of the rupture of a vas vasorum but the intima quickly breaks through into the medial lesion by tearing sharply in a horizontal or oblique direction part way around the inner circumference of the aorta in its ascending portion or in the arch less commonly in its descending portion in thorax or abdomen (Figure 147 page 774) Under a high head of pressure (most of the patients have hypertension) the intra aortic blood penetrates into the media as a rule splits it extensively up and down but sometimes only up or down and occasionally dissects its entire length from aortic valve to bifurcation at the common iliac arteries The dissection occurs around  $\frac{1}{2}$  to  $\frac{3}{4}$  of the circumference of the aorta and the blood in the medial split bulges the wall out in a variable but usually only moderate extent of  $\frac{1}{2}$  to 1 cm thickness Secondary tears through the intima are likely to be found at the upper and lower ends of the dissection even into one of the iliac arteries thus producing an extra channel through which the blood passes In most cases in the course of minutes hours or days the aorta ruptures completely as the result of a tear through the adventitia with sudden death due to extensive hemorrhage into pericardial or pleural cavity in a few cases the lesion heals sufficiently so that the extra aortic channel becomes lined with endothelium to give a double barreled aorta A constant and important complication is the involvement in the process of dissection of the mouths of the aortic branches with compression of these vessels and resulting effects of the sudden blocking of the local circulation as in the case of an iliac a coronary or an intercostal artery

Careful search of the aortic wall histologically at the site of rupture has revealed in most cases an area of unexplained degeneration or necrosis in the media

**Symptoms** In a few cases the arterial dissection may apparently be either symptomless or so obscure in its symptomatology that it cannot be diagnosed As a rule however there are two symptoms that are more or less characteristic and when added together almost pathognomonic Pain attending the splitting of the aortic wall is usually excruciating and extensive radiating from mid thorax front or back through the chest down the back and even into the thighs or up into the neck The pain in the thorax or back comes suddenly at its maximum and is often prostrating inducing a state of shock or even death If the patient survives the pain usually lasts for hours sometimes 24 to 48 hours requiring morphine repeatedly it may recur if there is an extension of the dissection

The other important symptom or group of symptoms is dependent on the blocking of the circulation to some important part or parts of the body especially legs viscera or brain Pain numbness coma and other symptoms may result The very multiplicity of symptoms in some cases aids in the diagnosis

**Signs** There are no pathognomonic signs of dissecting aneurysms. In the case of the aorta a systolic murmur at the base of the heart transmitted ■ neck and along the spine may be heard and an aortic diastolic murmur has been noted but these murmurs are far from constant. Chronic hypertension and some cardiac enlargement therefrom are almost invariably present. The

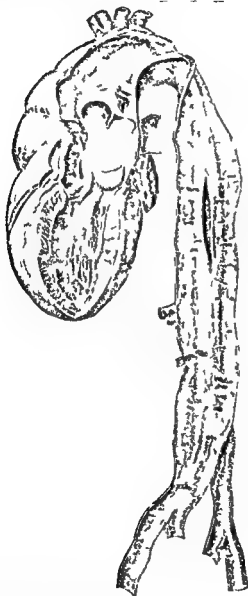


FIG 147 Drawing showing dissecting aneurysm of the aorta beginning in the ascending aorta and extending the entire length of the aorta into the common iliac. (W G MacCallum *A Text book of Pathology* 1928 W B Saunders Company Philadelphia )

blood pressure often remains high after the dissection occurs or it may sink rapidly and to a low level temporarily during the state of vascular shock that commonly appears and may rise again with recovery. Arterial pulse obliteration may be found due to compression of one of the aortic branches; this is most commonly observed in the legs where other signs of vascular occlusion develop.

Fever and leukocytosis of slight to moderate degree are common for a few days or of low grade even for a few weeks after the dissection of the aortic wall.

Roentgen ray examination is rarely helpful unless a comparison of the shape and size of the aorta in a film taken before the acute illness can be accurately made with the aortic shape and size after the occurrence of the dissecting aneurysm. Slight changes in shape and caliber are to be expected. Very rarely a larger bulge than usual of the dissected aortic wall may be noted by roentgen ray with calcified aortic intima visible well within this shadow.

Electrocardiography is helpful because of its negative findings except in rare cases where one or the other or both coronary arteries may be involved in the process with more or less occlusion. Usually the electrocardiogram shows no striking change from records taken prior to the acute illness. Such records may be expected to show in some cases the hypertensive pattern (see Chapter 19).

**Course and prognosis.** Dissecting aneurysms of the aorta are usually fatal the result of rupture through the adventitia in the course of minutes to days in three quarters to four fifths of the cases. Death in such individuals occurs suddenly even though they may seem to be convalescing satisfactorily. Certain cases survive a few months to a few years and may die noncardiovascular deaths. In some of these the postmortem finding of a double barreled aorta has been a complete surprise. Sudden death has been reported from spontaneous rupture and dissecting aneurysm of the left anterior descending coronary artery with compression and complete occlusion of the lumen (Helpern 1947).

**Complications.** As noted above the chief complications of dissecting aneurysms are external fatal rupture and blocking of the circulation to some part of the body (especially legs, heart and brain).

**Treatment.** So far the only treatment for dissecting aneurysms is absolute rest for weeks, probably six at least, special nursing care at the onset of the acute illness and symptomatic therapy by morphine for pain and shock and for symptoms due to obstruction of various peripheral or visceral arteries. No surgical therapy appears justified as yet.

**Differential diagnosis.** There are two conditions particularly with which dissecting aneurysm of the aorta is likely to be confused: coronary thrombosis and peripheral embolism. The intense thoracic pain followed frequently by a state of vascular shock with drop in blood pressure and later by fever and leukocytosis strongly suggests acute coronary occlusion, but there are certain clues usually present which point to the correct diagnosis: the sudden onset of the maximal pain instead of the building up of the pain in the course of a



few minutes as is the case with coronary occlusion pain the radiation of the pain usually to the back or its original presence there the radiation of the pain down the back often to the legs the evidence of rapid blocking of peripheral arteries before embolism from endocardial infarction is possible and the usual absence of characteristic coronary changes in the electrocardiogram Dissecting aortic aneurysm as a cause of blocking of the peripheral arteries can be distinguished from embolism by the initial occurrence of severe chest or back pain just prior to the arterial block (by only a few minutes) and the absence of any adequate explanation for intracardiac thrombosis where the embolus would have to originate

Pulmonary embolism, another thoracic emergency is less likely to be confused with dissecting aneurysm of the aorta because of the preponderant dyspnea cyanosis and tachycardia attending it with much less pain a frequent story of recent operation or injury the common occurrence of phlebothrombosis in the legs and the occasional bloodspitting and localized pulmonary signs

### ARTERIOVENOUS ANEURYSMS

An important vascular lesion uncommon but of considerable interest is a direct communication between artery and vein this is called an arteriovenous aneurysm or fistula It does not include the small vessels which normally may join arterioles directly to venules without the interposition of capillaries that have been found in certain parts of the body as in the fingers (Grant and Bland 1931) and in the myocardium (Wearn et al 1933) Although an arteriovenous aneurysm may occur anywhere in the body and between vessels of any size it is most common in the extremities between arteries and veins of medium caliber like the popliteal vessels Usually trauma is the cause a perforating wound uniting an artery with a vein either directly or by rupture of traumatic aneurysm hematoma or infected area Such a fistula may result accidentally from surgical operation Much less often primary arterial disease namely infection ulceration or aneurysm is responsible as in the case of the rupture of an aneurysm of the ascending aorta into the superior vena cava A congenital arteriovenous aneurysm is not so rare as was once thought it is an infrequent but important anomaly of the pulmonary circulation resulting in cyanosis and cardiac enlargement

The short circuit of a considerable amount of blood produced by a large arteriovenous aneurysmal shunt has three chief effects In the first place the vein is widely dilated the dilatation extending generally far along the course of the vein distending the valves if present and rendering the vein incompetent There is seen and felt a marked arterial pulse in the vein and a blocking of venous blood flow occurs distal to the aneurysm The artery also takes part in the dilatation but to a much smaller degree In the second place a loud often roaring continuous murmur with systolic accentuation and a palpable continuous thrill is evident over an arteriovenous aneurysm of large or average size even when it is deep-seated These signs are the chief basis for the

diagnosis In the third place the lesion may be serious because of the effect on the heart the left ventricle becoming considerably enlarged except when the arteriovenous aneurysm is small The blood flow is much increased by an arteriovenous shunt of large size and it is this fact that is doubtless responsible for the effect on the heart

An interesting lesion which like patency of the ductus arteriosus has an effect on the heart and circulation similar to that of an arteriovenous aneurysm or shunt is perforation of the aorta into the pulmonary artery—here the blood stream goes from the high pressure systemic circulation into the low pressure pulmonary circulation with deleterious effect death if the perforation is large heart failure if small

The course and prognosis are unfavorable with arteriovenous aneurysms of large size unless they can be treated heart failure developing in the course of a few months or years A communication between aorta and superior vena cava is especially serious death coming as a rule quickly in a few hours days or weeks Rupture of the arteriovenous aneurysm is an occasional complication

The treatment consists of ligation of the arteriovenous aneurysm about three months after the development of the lesion if traumatic (to allow the establishment of an adequate collateral circulation) if such ligation is possible Rapid relief usually follows ligation with decrease or disappearance of cardiac enlargement and prevention of heart failure A case of cure of Streptococcus viridans infection of an arteriovenous aneurysm by excision of the aneurysm was reported by Hamman and Rienhoff in 1935

### PERIPHERAL VASCULAR DISEASE

Although peripheral vascular disease is often set off by itself as a special province and is per se widely spread throughout the entire body nevertheless it forms but a part of the larger realm of cardiovascular disease and has frequent and intimate associations with diseases of the heart and great vessels

### DISEASES OF ARTERIES

Some of the more intimate associations have already been referred to such as *periarteritis nodosa* which is in reality a systemic disease involving many parts of the body including the coronary arteries damage to which can seriously affect the heart (see Chapters 21 and 23) Arterial obstruction by *thrombosis* superimposed on *sclerotic disease* or *endarteritis obliterans* (Buerger's disease) can jeopardize the health and result in gangrene of the legs especially in men already laboring under the strain of some type of heart disease usually coronary or hypertensive or both and *arterial embolism* may be a serious complication and even precipitate death in patients with rheumatic heart disease subacute bacterial endocarditis and coronary heart disease (see Chapters 14 15 and 21) On the other hand *intermittent claudication* which consists of leg muscle ache especially in the calves on walking due to insufficient blood supply secondary to arterial obstruction may limit the activity of

a patient with coronary insufficiency to such degree that this more important disease is less of a hazard to life *Endarterectomy* recently introduced in France (Leriche 1946 Bazy 1948 Laubry and Reboul 1950) has been an effective new therapeutic measure helping certain cases of arterial obstruction much more than have vasodilating agents and sympathectomy although aminophylline has helped some cases (Kassin et al 1951)

*Arterial spasm* is an occasional disturbing accompaniment of venous thrombosis in the extremities or of arterial embolism and as a special entity produces the important condition of *Raynaud's disease* (Raynaud 1862) which giving rise at first to the syndrome of dead fingers (*doigts morts*) can progress to serious structural changes in the tissues and even to gangrene (see Chapter 31) There is still some question as to whether either arterial spasm or *endarteritis obliterans* of the Buerger type affects the coronary circulation

*Arteriosclerosis of the media* of the arteries of the limbs so often found in laborers and called *Monckeberg's sclerosis* (Monckeberg 1924), is an entirely different process from the atherosclerosis of coronary and cerebral arteries and aorta as a matter of fact I have very infrequently found tortuous calcified and beaded radial arteries in my patients with coronary heart disease whose radials are usually soft and similarly have infrequently noted coronary heart disease in cases with Monckeberg's peripheral arterial sclerosis

*Aneurysms sacular* due to syphilis mycotic involvement arteriosclerosis and trauma *dissecting* and *arteriovenous* all of which may have an important effect on heart and great vessels have been discussed in some detail earlier in this chapter

## DISEASES OF VEINS

The most common diseases of the veins are *thrombosis* and *varicosities*. The former in its most important relationship of leg vein thrombosis has been discussed earlier in this chapter in the section on Pulmonary Embolism another important though rare abnormality is that of thrombosis of the great veins particularly the *venae cavae* an example of which is illustrated in Figure 148 Pressure by surrounding structures (e.g. tumors) trauma infection and stasis are causative factors if the superior vena cava is blocked the so-called superior mediastinal syndrome results and if the inferior vena cava is thrombosed high up there develops the inferior mediastinal syndrome Varicose veins are more of a nuisance than a serious disease but on occasion they may be associated with ulceration and infection and when very extensive may actually give rise to circulatory insufficiency due to the pooling of enough blood in huge varicose veins so that there is a serious reduction of the volume of blood returned to the heart with resulting faintness and dizziness (Chapman and Asmussen 1942) *Venous spasm* is an interesting phenomenon which may on occasion cause difficulty as in occasional instances of cardiac catheterization

Portal and splenic vein thrombosis can be very serious with obstruction and ascites resulting therefrom as also from hepatic cirrhosis which may require consideration of portocaval anastomosis via renal circulation or vena cava

directly One of the important complications of such diseases is dilatation of the esophageal varices that are so prone to bleed freely

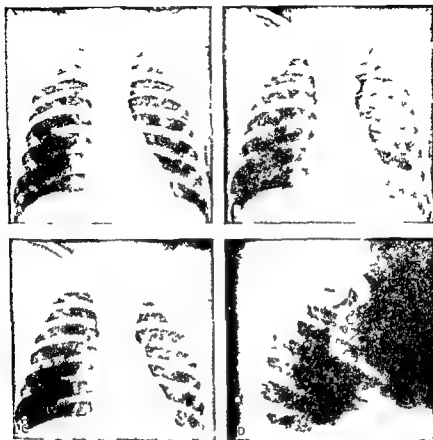


FIG 148 Roentgenograms of thorax showing visualization of great veins by Diodrast injection Case of young man with traumatic block of superior vena cava indicated clearly in (B) and not visualized in the control record (A) (C) Film taken shortly after (B) showing filling of vena azygos minor and a pericardial vein (D) Oblique view shows very well the large collateral vessel vena azygos minor taking blood from the upper superior vena cava down to the abdomen to empty into the inferior vena cava (With the kind help of Dr George P Robb 1 Madison Ave New York City)

For further discussion and details of the etiology diagnosis and treatment of peripheral vascular disease the reader is referred to the references to publications in the Bibliography at the end of this chapter

## BIBLIOGRAPHY

### VASCULAR DISEASE

Diseases of the Aorta (See also references in Chapters 13 Congenital Cardiovascular Defects 16 Cardiovascular Syphilis 23 Section on Trauma and Sections on Aneurysms of the present chapter)

- Bayley R. H. "Dynamic Dilatation of the Thoracic Aorta" *Am Heart J* 1933 VIII, 585
- Erdheim J. "Medionecrosis aortae idiopathica" *Virch Arch f path Anat* 1919 CCLXXIII 454
- Fry F. W. "Embolism and Thrombosis of the Abdominal Aorta" *Mod Concepts Cardiovas Dis* 1940 IX No 5
- Harris R. R. "Spontaneous Rupture of the Aorta" *J Iowa State M Soc* 1938 XXVIII, 453
- Hvilivitzkaja M. I. "Über die postmortale Contractilität der menschlichen Aorta" *Virch Arch f path Anat* 1928 CCLXVIII 758
- Leary T. "Atherosclerosis: Special Consideration of Aortic Lesions" *Arch Path* 1936 XXI 419
- Lundberg A. "Three Cases of Healed Aortic Rupture" *Acta med Scandinav* 1930 LXXIII 19
- Maresch R. "Ueber eitrige Aortitis" *Wien klin Wchnschr* 1926 XXXIX 1078
- Neibach J. H. and Herrington L. P. "The Significance of the Tensility of the Aorta as an Index of the Aging Process in the Animal Body" *Am Heart J* 1941 XXII, 661
- Palmer R. S. "A Case of Marked Tortuosity of the Abdominal Aorta without Calcification Causing Mild Attacks of Subacute Intestinal Obstruction" *Ann Int Med* 1942 XVII 358
- Perry T. M. "Incomplete Rupture of the Aorta" *Arch Int Med* 1942 LXX 689
- Roesler H. and White P. D. "Unusual Variations in the Roentgen Shadow of the Elongated Thoracic Aorta" *Am Heart J* 1931 VI 768

#### Recent References (1944-1950)

- Burford T. H. and Carson M. J. "Visualization of the Aorta and Its Branches by Retroarterial Diodrast Injection" *J Pediat* 1948 XXXIII 675
- Burgess C. M. and Hartwell A. S. "Removal of Saddle Embolus of Aorta" *JAMA* 1949 CXLI 387
- Gross R. E. and Ware P. F. "Surgical Significance of Aortic Arch Anomalies" *Surg Gynec & Obst* 1946 LXXXIII, 435
- Jackman J. and Lubert M. "The Significance of Calcification in the Ascending Aorta as Observed Roentgenologically" *Am J Roentgenol* 1945 LIII 432
- Jokl E. and Mackintosh R. H. "Sudden Death of Young Athlete from Rupture of Ascending Aorta" *Lancet* 1950 II 54
- Lansing A. I., Alex M. and Rosenthal T. B. "Atheromatosis as a Sequel to Seroscent Changes in the Arterial Wall" *J Gerontol* 1950 V 314
- Levinson D. C., Edmeades D. T. and Griffith G. C. "Dissecting Aneurysm of the Aorta: Its Clinical, Electrocardiographic and Laboratory Features. A Report of Fifty-eight Autopsied Cases" *Circulation* 1950 I 360
- Taylor F. H. and Morehead R. P. "Spontaneous Complete Rupture of the Aorta Without Dissecting Aneurysm with Report of a Case Showing a New Physical Sign (Periaortic Friction Rub)" *Ann Int Med* 1944 XXI 11
- Wilson H. "Aortic Embolectomy: Successful Removal of Saddle Embolism by Transabdominal Route" *JAMA* 1949 CXLI 389

#### Diseases of the Pulmonary Artery and Pulmonary Embolism (See also references in Chapter 20 Pulmonary Heart Disease)

- Barber N. W., Nygaard K. K., Walters W. and Priestley J. T. "A Statistical Study of Postoperative Venous Thrombosis and Pulmonary Embolism" *Proc Staff Meet Mayo Clin* 1940 XV 769 1941 XVI 1 17 33
- Barnes A. R. "Pulmonary Embolism" *JAMA* 1937 CIX 1347
- Brenner O. "The Pathology of the Vessels of the Pulmonary Circulation" *Arch Int Med* 1935 LVI 211 457 724 976 and 1189
- Burwinkel O. "Die Zunahme von Lungenembolien" *Munch med Wchnschr* 1915 LXXV 1129
- Castleman H. "Healed Pulmonary Infarcts" *Arch Path* 1940 XXX 130
- Costa A. "Sulla frequenza distribuzione e genesi dell'arteriosclerosi nel tronco dell'

- arteria pulmonale in base a ricerche istopatologiche sistematiche" *Clin med ital* 1927 LVIII 325
- Currens J., and Barnes A H "The Heart in Pulmonary Embolism" *Arch Int Med* 1943 LXXI 325
- de Takats G and Jesser J H "Pulmonary Embolism Suggestions for Its Diagnosis Prevention and Management" *JAMA* 1940 CXIV 1415
- Fine J and Sears J B "Prophylaxis of Pulmonary Embolism by Division of Femoral Veins" *Ann Surg* 1941 CXIV 801
- Giroux L *Sclerose et atherome de l'artere pulmonaire Role des conditions mecaniques* G Steinheil Paris 1910
- Hampton A O and Castleman B "Correlation of Postmortem Chest Teleroentigenograms with Autopsy Findings with Special Reference to Pulmonary Embolism and Infarction" *Am J Roentgenol* 1940 XLIII 305
- Hanelin J and Eyer W R "Pulmonary Artery Thrombosis: Roentgen Manifestations" *Radiology* 1951 LVI 689
- Henderson E F "Fatal Pulmonary Embolism A Statistical Review" *Arch Surg* 1917 XV 231
- Homans J "Pulmonary Embolism Due to Quiet Venous Thromboses and Simulating Cardiac and Pulmonary Disease" *New England J Med* 1943 CCXXIX 309
- Horine C F and Warner C G "Distribution of Pulmonary and Bronchial Circulation Experimental Study" *J Thoracic Surg* 1931 II 80
- Kinsey D and White P D "Fever in Congestive Heart Failure" *Arch Int Med* 1940 LXV 163
- Kirschner M "Ein durch die Trendelenburgsche Operation geheilter Fall von Embolie der Art pulmonalis" *Arch f klin Chir* 1924 CXXXIII 312
- Levine H B and White P D "Pulmonary Infarction Complicating Severe Disease of Mitral Valve" *Arch Int Med* 1937 LX 39
- McGinn S and White P D "Acute Cor Pulmonale Resulting from Pulmonary Embolism" *JAMA* 1935 CIV 1473
- Murnaghan D McGinn S and White P D "Pulmonary Embolism with and without the Acute Cor Pulmonale with Especial Reference to the Electrocardiogram" *Am Heart J* 1943 XXV 573
- Nystrom G "Experiences with the Trendelenburg Operation for Pulmonary Embolism" *Ann Surg* 1930 XCII 498
- Scherf D and Schonbrunner E "Uber Herzbefunde bei Lungenembolien" *Ztschr f klin Med* 1935 CCXVIII 455
- Trendelenburg F "Ueber die operative Behandlung der Embolie der Lungenarterie" *Verhandl d deutsch Gesellsch f Chir* 1908 II 89
- Westdahl P R "Pulmonary Embolism Study of 247 Cases" *West J Surg* 1941 XLIX 77
- White P D "Pulmonary Embolism and Heart Disease" *Am J M Sc* 1940 CC 577

#### Recent References (1944-1950)

- Baker D V Jr Warren R Homans J and Littman D "Pulmonary Embolism Evaluation of a Policy for Prophylaxis and Therapy" *New England J Med* 1950 CCXLII 923
- Carlotti J Hardy I B Jr Linton R R and White P D "Pulmonary Embolism in Medical Patients A Comparison of Incidence Diagnosis and the Effects of Treatment of 773 Cases at the Massachusetts General Hospital in Two Five Year Periods (1936 to 1940 and 1941 to 1945 Inclusive)" *Am Heart J* 1947 XXXIII 737
- Collins D H "Bullet Embolism Case of Pulmonary Embolism Following Entry of Bullet Into Right Ventricle of Heart" *J Path & Bact* 1948 LX 205
- Dack S Master A M Horn H Grishman A and Field L E "Acute Coronary Insufficiency Due to Pulmonary Embolism" *Am J Med* 1949 VII 464
- Newberger C "Maternal Pulmonary Embolism by Amniotic Fluid" *Illinois M J* 1950 XCVIII 301
- Roe B B and Goldthwaite J C "Pulmonary Embolism A Statistical Study of Post Mortem Material at the Massachusetts General Hospital" *New England J Med* 1949 CCXLI 679

- Shapiro R and Rigler L G Pulmonary Embolism without Infarction *Am J Roentgenol* 1948 LX 460
- Vanderveer J H Kuo P T and Marshall D S Experiences with Venous Thrombosis and Pulmonary Embolism with Special Reference to Anticoagulant Therapy *Am J M Sc* 1950 CCXIX 117
- White H B "The Continuing Challenge of Pulmonary Embolism" Editorial *New England J Med* 1949 CCXLI 719

**Communications between the Aorta and Pulmonary Artery** (See references in Chapter 13 Congenital Cardiovascular Defects and under Aneurysms in present chapter)

#### Arterial Aneurysms (General References)

- Crisp E A *Treatise on the Structure Diseases and Injuries of the Blood Vessels with Statistical Deductions* John Churchill London 1847
- Klotz O *Concerning Aneurysms* The Third Gordon Bell Memorial Lecture delivered before the Winnipeg Medical Society April 1 1926 Univ of Toronto Press 19 6
- Lucke B and Rea M H Studies on Aneurysm I General Statistical Data on Aneurysms *JAMA* 1921 LXXVII 935
- Matas H "Operation for the Radical Cure of Aneurysm Based Upon Arteriorrhaphy with the Report of Four Cases Successfully Operated Upon by the Author" *Tr Am S A* 1902 XX 396
- Morgagni G H *De Sedibus et Causis Morborum* Ex typog Remondiniana Venice 1761
- Reid M R Aneurysms in the Johns Hopkins Hospital All Cases Treated in the Surgical Service from the Opening of the Hospital to January 1922" *Arch Surg* 19 6 XII 1

#### Recent References (1944-1950)

- Elkin H C "Aneurysm Following Surgical Procedures Report of Five Cases" *Ann Surg* 1948 CXXXVII 769
- Poppe J K and de Oliveira H R "Treatment of Syphilitic Aneurysms by Cellophane Wrapping" *J Thoracic Surg* 1946 XV 185
- Revell S T R Jr "Primary Mycotic Aneurysms" *Ann Int Med* 1945 XXII 431
- Shafiroff B G P and Kau Q Y "Cellophane Wrapping of Intrathoracic Aneurysms" *New York State J Med* 1950 L 1479

#### Aortic Aneurysms (See later for Dissecting Aneurysms)

- Boyd L J "A Study of Four Thousand Reported Cases of Aneurysm of the Thoracic Aorta" *Am J M Sc* 1924 CLXVIII 654
- Crawford J H "Bilateral Pulse Obliteration in Thoracic Aneurysm" *JAMA* 19 1 LXXVI 1395
- Kampmeier R H "Saccular Aneurysm of the Thoracic Aorta A Clinical Study of 633 Cases" *Ann Int Med* 1938 XII 624
- Lucke B and Rea, M H Studies on Aneurysm. II Aneurysms of the Aorta *JAMA* 1923 LXXXI 1167
- Osler W "Aneurysm of the Abdominal Aorta" *Lancet* 1905 II 1089
- Porter W B "The Syndrome of Rupture of Aortic Aneurysm into the Pulmonary Artery" *Tr A Am Physicians* 1941 LVI 201 and *Am Heart J* 1947 XXIII 468
- Ruffin M deG Castleman B and White H D "Arteriosclerotic Aneurysms and Senile Ectasia of the Thoracic Aorta" *Am Heart J* 1941 XXII 458
- Sanford S P "Thoracic Aneurysm" *Ann Int Med* 1931 IV 1417
- Scott E W "Aortic Aneurysm Rupturing into the Pulmonary Artery Report of Two Cases" *JAMA* 1924 LXXXII 1417
- Wade W F "On a Case of Aortic Aneurysm in Which a Communication with the Pulmonary Artery Was Recognized During Life" *M Chir Tr London* 1861 XLIV 211
- White J C "Painful Aneurysms of the Aortic Arch Relief by Paravertebral Injections of Procaine and Alcohol" *JAMA* 1932 XCIX 10
- White P D Chamberlain F L and Kelson S "Rupture of Aorta into the Pulmonary Artery with Long Survival" *Ann Int Med* 1941 XV 589

## Recent References (1944-1950)

- Abbott, O A "Clinical Experiences with the Application of Polythene Cellophane Upon Aneurysms of the Thoracic Vessels" *J Thoracic Surg* 1949 XVIII 435
- Cowley II A Sloan II E and Sullenberger II "Successful Repair of Aortic Aneurysm with Sternal Perforation" *J Thoracic Surg* 1951 XXI 159
- Eichler B II and Heller S N "Aneurysm of Aorta with Compression of Pulmonary Artery and Left Auricle" *Ann Int Med* 1945 XXIII 652
- Estes J E Jr "Abdominal Aortic Aneurysm A Study of One Hundred and Two Cases" *Circulation* 1950 II 258
- Jones A M., and Langley F A "Aortic Sinus Aneurysms" *Brit Heart J* 1949 XI 325
- Monod O., and Meyer A "Resection of an Aneurysm of the Arch of the Aorta with Preservation of the Lumen of the Vessel" *Circulation* 1950 I 220
- Owens J N Jr and Bass A D "Tuberculous Aneurysm of Abdominal Aorta Report of Case" *Arch Int Med* 1944 LXXIV 413
- Scott V "Abdominal Aneurysms Report of 96 Cases" *Am J Syph Gonorr & Ven Dis* 1944 XXVIII 682
- Sison A G and Campos P C "Adams Stokes Syndrome Resulting from an Aortic Aneurysm That Ruptured into the Interventricular Septum Report of a Case" *Acta med Philippina* 1948 IV No 4
- Swan H Maaske C Johnson M and Grover R "Arterial Homografts II Resection of Thoracic Aortic Aneurysm Using a Stored Human Arterial Transplant" *Arch Surg* 1950 LXI 738

## Aneurysms of Pulmonary Artery

- Boyd L J "Aneurysm of the Trunk and Main Branches of the Pulmonary Artery Analysis of 152 Cases" *Mod Concepts Cardiovas Dis* 1941 X No 2
- Deterling R A Jr and Clagett O T "Aneurysm of the Pulmonary Artery Review of the Literature and Report of a Case" *Am Heart J* 1947 XXXIV 471
- Warthin A S "Syphilis of the Pulmonary Artery Syphilitic Aneurysm of Left Upper Division Demonstration of Spirochete Pallida in Wall of Artery and Aneurysmal Sac" *Am J Syph* 1917 I 693
- Wilkinson K D "Aneurysmal Dilatation of the Pulmonary Artery" *Brit Heart J* 1940 II 255

## Aneurysms of Other Arteries

- Globus J H and Schwab J M "Intracranial Aneurysms Their Origin and Clinical Behavior in a Series of Verified Cases" *J Mt Sinai Hosp* 1947 VIII 547
- Rigdon R H and Vandergrieff II "Aneurysms of Coronary Arteries Review of Literature and Report of Case" *Am J Surg* 1943 LXI 407
- Short D W "Occupational Aneurysm of the Palmar Arch Report of Case" *Lancet* 1948 II 217
- Tonge J I "Aneurysms of Splenic Artery with Report of Two Cases and Review of Literature" *M J Australia* 1948 II 119

## Dissecting Aneurysms

- Cleland J B "Healed Dissecting Aneurysm Giving Rise to the Appearance of a Double Aorta" *M J Australia* 1927 I 538
- Harstad K "Spontaneous Rupture of Aorta with Dissecting Aneurysm in Boy Aged 14" *Norsk mag f laegevid* 1938 XCIX 1311
- Mote C D and Carr J L "Dissecting Aneurysm of Aorta" *Am Heart J* 1942 XXIV 69
- Peacock R II "An Account of Some Experiments Illustrative of the Mode of Formation of Dissecting Aneurysms" *London & Edinburgh Monthly J Med & Surg* 1843 III 871
- Shennan T "Dissecting Aneurysms" Medical Research Council Special Report Series No 193 London His Majesty's Stationery Office 1934
- White P D Castleman II and Badger T L "Dissecting Aortic Aneurysm Wrongly Diagnosed Coronary Thrombosis" *JAMA* 1934 CIII 1135



*Recent References (1944-1950)*

- Baer S and Goldburgh H L The Varied Clinical Syndromes Produced by Dissecting Aneurysm *Am Heart J* 1948 XXXV 198
- David P McPeak E M Vivas Salas E and White P D Dissecting Aneurysm of the Aorta A Review of 17 Autopsied Cases of Acute Dissecting Aneurysm of the Aorta Encountered at the Massachusetts General Hospital from 1937 to 1946 Inclusive Eight of Which Were Correctly Diagnosed Antemortem *Ann Int Med* 1947 XXVII 405
- Helpern M "Sudden Death from Spontaneous Rupture and Dissecting Aneurysm of a Coronary Artery *Proc New York Path Soc* Nov 26 1947
- Leonard D W Dissecting Aneurysm of the Thoracic Aorta Due to Trauma *Am J Surg* 1945 LXIX 344
- McLaurin J W Dissecting Aneurysm of the Aorta in a Boy *New Orleans M & S J* 1945 XCVII 317
- Scott R W and Sancetta S M Dissecting Aneurysm of Aorta with Hemorrhagic Infarction of the Spinal Cord and Complete Paraplegia *Am Heart J* 1949 XXXVIII 747
- Wainwright C W "Dissecting Aneurysm Producing Coronary Occlusion by Dissection of Coronary Artery *Bull Johns Hopkins Hosp* 1944 LXXV 81

*Arteriovenous Aneurysms*

- Grant R T and Bland E F Observations on Arteriovenous Anastomoses in Human Skin and in the Bird's Foot with Special Reference to the Reaction to Cold *Heart* 1931 XV 385
- Hamman L and Rienhoff W F Jr "Subacute Streptococcus Viridans Septicemia Cured by Excision of an Arteriovenous Aneurysm of External Iliac Artery and Vein. *Bull Johns Hopkins Hosp* 1935 LVII 219
- Matas R Herrmann G and Reid M R Effect of Arteriovenous Aneurysms ■ Heart Report of Case Studied *Ann Surg* 1932 XCV 578
- Osler W "Remarks on Arterio Venous Aneurysm *Lancet* 1915 I 949
- Reid M R "The Effect of Arteriovenous Fistula upon the Heart and Blood Vessels An Experimental and Clinical Study *Bull Johns Hopkins Hosp* 1920 XXXI 43
- Wearn J T Mettler ■ R Klumpp T G and Zschiesche L J The Nature of the Vascular Communications Between the Coronary Arteries and the Chambers of the Heart *Am Heart J* 1933 IX 143

*Recent References (1944-1950)*

- Baer ■ Behrend A and Goldburgh H L Arteriovenous Fistulas of the Lungs *Circulation* 1950 I 602
- Beierwaltes W H and Byron F X Pulmonary Arteriovenous Aneurysm with Secondary Polycythemia Report of the First Case Treated by Lobectomy *JAMA* 1947 CXXXIV 1069
- Elkin D C Arteriovenous Aneurysm *JAMA* 1945 CXXIX 26
- Elkin D C and Warren J V "Arteriovenous Fistulas Their Effect on the Circulation. *JAMA* 1947 CXXXIV 1574
- Lindskog G E Liebow A Kausel ■ and Janzen A Pulmonary Arteriovenous Aneurysm *Ann Surg* 1950 CXXXII 591
- Linton R R and White P ■ "Arteriovenous Fistula Between Right Common Iliac Artery and Inferior Vena Cava Report of Case of Its Occurrence Following Operation for Ruptured Intervertebral Disk with Cure by Operation *Arch Surg* 1948 L 6
- Olivecrona H. and Rives J "Arteriovenous Aneurysms of Brain Their Diagnosis and Treatment *Arch Neurol & Psychiat* 1948 LIX 567

**Diseases of Other Arteries. General Arterial Disease Embolism and Thrombosis** (See also references in other parts of this chapter)

Albutt C *Diseases of the Arteries Including Angina Pectoris* Macmillan and Co Ltd London 1915

- Aschoff L. "Observations Concerning Relationship Between Cholesterol Metabolism and Vascular Disease" *Brit M J* 1932 II 1131
- Baggenstoss A H and Keith H M "Calcification of Arteries of Infant" *J Pediat* 1941 XVIII 95
- Barker N W and Roth G M "The Treatment of Occlusive Arterial Disease of the Legs by Means of the Sanders Vasoscillator (Sanders Bed)" *Am Heart J* 1939 XVIII 312
- Cowdry H V *Arteriosclerosis A Survey of the Problem* A Publication of the Josiah Macy Jr Foundation Macmillan Co New York 1933
- Geissendorfer R *Thrombose und Embolie Kritische Betrachtungen und Untersuchungen zur Frage der Thrombose und Embolie unter besonderer Berücksichtigung der sogenannten blinden Fernthrombose und tödlichen Lungenembolie* Johann Ambrosius Barth Leipzig 1935
- Giamarino H J and Jaffe S A Mesenteric Vascular Occlusion Review of Literature and General Principles Report of Case with Operation and Recovery *Arch Surg* 1947 XLV 647
- Gull W W and Sutton H G On the Pathology of the Morbid State Commonly Called Bright's Disease with Contracted Kidney (Arterio-capillary Fibrosis) *M Chir Tr London* 1872 LV 273
- Herrmann L G and Reid M R Passive Vascular Exercises Treatment of Peripheral Obliterative Arterial Disease by Rhythmic Alternation of Environmental Pressure *Arch Surg* 1934 XXIX 697
- Hirsch E F and Weinhouse S "Role of Lipids in Atherosclerosis" *Physiol Rev* 1943 XXIII 185
- Homans J *Circulatory Diseases of the Extremities* Macmillan Co New York 1939
- Jores L "Arterien" Section B of Herz und Gefäße Vol II of *Handbuch der speziellen pathologischen Anatomie und Histologie* Julius Springer Berlin 1924
- Key E "Über Embolektomie als Behandlungsmethode bei embolischen Zirkulationsstörungen der Extremitäten" *Acta chir Scandinav* 1922 LIV 339
- Laufman H and Scheinberg S Arterial and Venous Mesenteric Occlusion: Analysis of 44 Cases *Am J Surg* 1947 LVIII 84
- Leary T Arteriosclerosis *Bull New York Acad Med* 1941 XVII 887
- Lewis T *Vascular Disorders of the Limbs* Macmillan Co New York 1936
- Lewis T Pickering G W and Rothschild P Observations upon Muscular Pain in Intermittent Claudication *Heart* 1931 XV 359
- Linton R R Peripheral Arterial Embolism" *New England J Med* 1941 CLXXXIX 274
- Ma Callum W G "Arteriosclerosis" *Physiol Rev* 1922 II 70
- Monckeberg J G Arteriosklerose *Klin Wchnschr* 1924 III 1521
- Nystrom G Zur Prognose und Methodik der Embolektomie *Acta chir Scandinav* 1926 LX 229
- Raynaud A G M *De l'asphyxie locale et de la gangrene symetrique des extremités* Thèse Rignoux Paris 1862
- Sanders C H Cardiovascular and Peripheral Vascular Disease Treatment by Motorized Oscillating Bed *J A M A* 1936 CVI 916
- Sperling P *Über Embolien bei Endocarditis* Inaug Diss Berlin 1872
- White J C Vascular and Neurologic Lesions in Survivors of Shipwreck I Immersion Foot Syndrome Following Exposure to Cold *New England J Med* 1943 CCXXVIII 211

## Recent References (1944-1950)

- Abramson D I and Shumacker H B Jr Raynaud's Disease in Men *Am Heart J* 1947 XXXIII 500
- Allen E V Barker N W and Hines E A Jr *Peripheral Vascular Diseases* W B Saunders Co Philadelphia 1946
- Altamirano Orrego M Subarachnoid Hemorrhage *Rev méd de Chile* 1950 LXXVIII 297
- Andrus W D Peripheral Arterial Embolism With Particular Reference to Evaluation of Conservative Treatment" *Arch Surg* 1950 LX 611

- Bazy L. Sur l'endarterectomie desoblitérante *Mém acad de chir* 1948 LXXIV 109
- Cauldwell E W, Siekert R G, Lininger R E and Anson H J. Bronchial Arteries. Anatomic Study of 150 Human Cadavers *Surg Gynec & Obst* 1948 LXXXVI 395
- deBakey M E and Simeone F A. Battle Injuries of Arteries in World War II. Analysis of 2 471 Cases. *Ann Surg* 1946 CXXIII 534
- Elkin D C, Cooper F W Jr, Rohrer R H and others. Study of Peripheral Vascular Disease with Radioactive Isotopes *Surg Gynec & Obst* 1948 LXXXVII 1
- Field M H. "Medial Calcification of Arteries of Infants" *Arch Path* 1947 XLII 607
- Flory C M. Arterial Occlusions Produced by Emboli from Eroded Aortic Atheromatous Plaques *Am J Path* 1945 XXI 549
- Freeman N E, Leeds F H and Gardner R E. "Arterectomy in the Treatment of Intractable Pain Following Recovery from Acute Arterial Occlusion" *Am Heart J* 1949 XXXVIII 329
- Freeman N E and Miller E R. Retrograde Arteriography in the Diagnosis of Cardiovascular Lesions. I. Visualization of Aneurysms and Peripheral Arteries. *Ann Int Med* 1949 XXX 330
- Kissin M et al. The Effect of Drugs Used in the Treatment of Intermittent Claudication on the Exercise Tolerance of Individuals with Obliterating Arteriosclerosis *Angiology* 1951 II 217
- Laubry P and Reboul H. Endarteriectomie désoblitérante et neuro-endarteriectomie intramurale. I. *Congres Mondial de Cardiologie* Paris Sept 3-9 1950 J B Bailliere et Fils Paris 242
- Leriche R. "De l'arteriectomie dans les arterites oblitérantes des vieillards d'après 144 observations" *Bruxelles Med* 1946 XXVI 471
- Linton R R. Arteriosclerotic Popliteal Aneurysm. Report of 14 Patients Treated by Preliminary Lumbar Sympathetic Ganglionectomy and Aneurysmectomy *Surgery* 1949 XXVI 41
- Mendez, L, Saenz Arroyo L and Zajarías S. "Padecimientos vasculares del cerebro. Estudio basado sobre el examen del material del Instituto Nacional de Cardiología de México." *Arch Inst cardiol Mexico* 1950 XX 644
- Prusik B. A Method of Treatment of Obliterating Endarteritis with Trophic Lesions in the Extremities. The Eutrophic Effect of Niacin Derivatives. *Cardiologia* 1949 XIV 81
- Robinson G L and Hartley R. Acute Bacterial Endarteritis. *Brit Heart J* 1951 XIII 106
- Wright I S. *Vascular Diseases*. Year Book Publishers Chicago 1948
- Zak F G and Elias K. Embolization with Material from Atheromata. *Am J M Sc* 1949 CCXVIII 510

#### Periarteritis Nodosa (See also references under Chapter 23 Miscellaneous)

- Fishberg, A M. "Zur Kenntnis der Periarteritis nodosa insbesondere der Histopathogenese" *Virch Arch f path Anat* 1933 CCXL 483
- Grant R T. "Observations on Periarteritis Nodosa" *Clin Sc* 1940 IV 245
- Horton H T, Magath T B and Brown G E. "An Undescribed Form of Arteritis of Temporal Vessels" *Proc Staff Meet Mayo Clin* 1932 VII 700
- Kussmaul A and Maier E. "Ueber eine bisher nicht beschriebene eigenthümliche Arterienkrankung (Periarteritis nodosa) die mit Morbus Brightii und rapid fort schreit oder allgemeiner Muskellähmung einhergeht" *Deutsch Arch f klin Med* 1866 I 484
- Rich A M and Gregory J E. "Experimental Demonstration That Periarteritis Nodosa Is Manifestation of Hypersensitivity" *Bull Johns Hopkins Hosp* 1943 LXXII 65
- Weiss S and Mallory T B. "Acute Disseminated Lupus Erythematosus versus Periarteritis Nodosa Case" *New England J Med* 1938 CCXVIII 838

#### Recent References (1944-1950)

- Cooke W T, Cloake P C P, Govan A, D T and Colbeck J C. "Temporal Arteritis Generalized Vascular Disease" *Quart J Med* 1946 XV 47
- Gelfand M L and Arnoff S. "Periarteritis Nodosa—Possible Relation in the Increased Usage of Sulfonamides" *Ann Int Med* 1949 XXX 919

- Hejmancik M R Schofield N D and Herrmann G R "Allergic Cardiovascular Disease, with Report of Two Cases of Periarteritis Nodosa" *Am J M Sc* 1949 CCXVII 187
- Higgins W H "Periarteritis Nodosa Clinical Manifestations and Postmortem Findings with Report of Six Cases" *South M J* 1946 XXXIX 453
- Wold L E and Barker N W "Periarteritis Nodosa (Essential Polyarteritis) Clinical Data on 30 Cases Proved at Necropsy" *Minnesota Med* 1949 XXXII 715

### Thromboangitis Obliterans

- Brown G E and Allen E V *Thrombo-angitis Obliterans Clinical Physiology and Pathologic Studies* Mayo Clinic Monograph W B Saunders Co Philadelphia 1928
- Buerger L "The Pathological and Clinical Aspects of Thromboangitis Obliterans" *Am J M Sc* 1917 CLIV 319
- Fisher M D "Buerger's Disease in a Boy of Sixteen Years" *JAMA* 1945 CXXIX, 868
- Hamlin E Jr Warren R and Kennard H E "Thromboangitis Obliterans An Evaluation of Therapy with Special Reference to Lumbar Sympathectomy" *New England J Med* 1949 CCXLI 849
- Van Deelen T H and Wright I S "Thrombo-angitis Obliterans in Women" *Am Heart J* 1937 XIII 373
- Yater W M "Thrombo angitis Obliterans in Negroes" *Am Heart J* 1937 XIII 511

### Diseases of the Veins Capillaries and Lymphatics Venous Thrombosis and Anticoagulants (See also references under Chapter 8 Capillary Circulation)

- Allen A W Linton R R and Donaldson G A "Thrombosis and Embolism Review of 207 Patients Treated by Femoral Vein Interruption" *Ann Surg* 1943 CXVIII 728
- Allen M W Barker N W and Waugh J M "A Preparation from Spoiled Sweet Clover Which Prolongs Coagulation and Prothrombin Time of the Blood" *JAMA* 1942 CXX 1009
- Bauer G "Early Diagnosis of Venous Thrombosis by Means of Venography and Abortive Treatment with Heparin" *Acta med Scandinav* 1941 CVII 136
- Benda E "Venen" P 787 of *Herz und Gefasse Vol II of Handbuch der speziellen pathologischen Anatomie und Histologie* Julius Springer Berlin 1924
- Blalock A and Burwell C S "Thoracic Duct Lymph Pressure in Concretio Cordis Experimental Study" *J Lab & Clin Med* 1935 XXI 296
- Bollman J L and Preston F W "Effects of Experimental Administration of Dicoumarin" *JAMA* 1942 CXX 1021
- Chapman, E M and Asmussen E "On the Occurrence of Dyspnea Dizziness and Precordial Distress Occasioned by the Pooling of Blood in Varicose Veins" *J Clin Investigation* 1942 XXI 393
- Cooper W M "Treatment of Varicose Veins Study Based on a Series of More Than Thirty Five Thousand Injections of Various Sclerosing Solutions Given in Three Thousand and One Hundred and Sixty Four Cases and Two Hundred and Ninety Three Cases of Extensive and Recurrent Varicose Veins Treated by Preliminary Ambulatory Ligation and Subsequent Injections" *Ann Surg* 1934 XCIX 799
- Drinker C K and Yoffey J M *Lymphatics Lymph and Lymphoid Tissue* Harvard University Press Cambridge 1942
- Edwards E A "Orientation of Venous Valves in Relation to Body Surfaces" *Anat Rec* 1936 LXIV 369
- Genevrier "Du traitement des varices par les injections coagulantes concentrees de sels de quinine" *Bull soc med mil française* 1921 XV 169
- Gray H K and Skinner I C "Constrictive Occlusion of Superior Vena Cava Report of Three Cases in Which Patients Were Treated Surgically" *Surg Gyne and Obst* 1941 LXXII 923
- Gunther L "Intramuscular Pressure VI Physiology of Venopressor Mechanism" *U S Naval M Bull* 1943 XLI 414
- Hauswirth L and Eisenberg A A "Disseminated Venofibrosis (Phlebosclerosis) Its Clinicopathologic Significance" *Arch Path* 1931 XI 857
- Hornans J "Phlegmasia Alba Dolens and the Relation of the Lymphatics to Thrombophlebitis" *Am Heart J* 1932 VII 415

- "Thrombosis as a Complication of Venography" *JAMA* 1942 CXIX 136
- Hunter W C Sneed V D Robertson T D and Snyder H A C "Thrombosis of Deep Veins of Leg Its Clinical Significance as Exemplified in 351 Autopsies" *Arch Int Med* 1941 LXVIII 1
- Krebs J M "Routine Use of Bicycle Exercise for Prophylaxis of Postoperative Thrombophlebitis Preliminary Report" *Am J Obst & Gynec* 1942 XLIV 73
- Moschcowitz E "Phleboscrosis of the Hepatic Veins as Associated with Chronic Passive Congestion of Liver and Cardiac Cirrhosis Preliminary Report" *Libman Anniversary Volumes* 1932 II 857
- Murray D W G et al "Heparin and the Thrombosis of Veins Following Injury" *Surgery* 1937 II 163
- Ochsner A and deBakey M "Therapy of Phlebothrombosis and Thrombophlebitis" *Arch Surg* 1940 XL 208
- Rousselot L M "The Role of Congestion (Portal Hypertension) in So Called Bantia Syndrome A Clinical and Pathological Study of Thirty-one Cases with the Late Results Following Splenectomy" *JAMA* 1936 CVII 1788
- Veal J R and Hussey H H "Thrombosis of the Subclavian and Axillary Veins" *Am Heart J* 1943 XXV 355
- Wright I S and Prandoni A "The Dicoumarin 3,3 Methylene Bis (4 Hydroxycoumarin) Its Pharmacologic and Therapeutic Action in Man" *JAMA* 1947 CXV 1015

#### Recent References (1944-1950)

- Alexander B deVries A and Goldstein R "Prothrombin A Critique of Methods for Its Determination and Their Clinical Significance" *New England J Med* 1949 CCXL 403
- Allen A W "Present Evaluation of Prophylaxis and Treatment of Venous Thrombosis and Pulmonary Embolism" *Surgery* 1949 XXVI 1
- Allen H V "The Clinical Use of Anticoagulants Report of Treatment with Dicoumarol in 1 686 Postoperative Cases" *JAMA* 1947 CXXXIV 323
- Bauer H "Heparin in Venous Thrombosis" *JAMA* 1946 CXXXI 196
- "Nine Years Experience with Heparin in Acute Venous Thrombosis" *Angiology* 1950 I 161
- Blakemore A H "Portacaval Anastomosis Report on Fourteen Cases" *Bull New York Acad Med* 1946 XXII 254
- "Portacaval Anastomosis for Portal Hypertension" *Surgery* 1949 XXVI 99
- Burke G E and Wright I S "Tromexan—3,3 Carboxymethylenebis (4 Hydroxycoumarin) Ethyl Ester Experimental and Clinical Properties" *Circulation* 1951 III 164
- Coleman F C "The Prothrombin Time in Dicoumarol Therapy" *Ann Int Med* 1949 XXX 895
- Collins C G Nelson E W Jones J H and others "Ligation of the Vena Cava Critical Evaluation Based on a Study of Twenty-two Cases" *New Orleans M & S J* 1947 XCIX 488
- Duff I F and Shull W H "Dicoumarol Poisoning" *JAMA* 1949 CXXXIX 76
- Glushien A H and Mansuy M M "Superior Vena Caval Obstruction with Survival after Thirty-six Years" *Angiology* 1951 II 210
- Goldfeder A Bloom H and Weiner H "A New Improved Method for Determination of Prothrombin Levels in Blood" *Science* 1950 CXI 365
- Johnson J Kirby C K Greifenstein F E and Castillo A "Experimental and Clinical Use of Vein Grafts to Replace Defects of Large Arteries" *Surgery* 1949 XXVI 945
- Jorpes E "Five Years of Specific Therapy of Thrombosis in Sweden" *Nord med* 1946 XXX 813
- Kety H H "Measurement of Regional Circulation by the Local Clearance of Radioactive Sodium" *Am Heart J* 1949 XXXVIII 321
- Lilly G D and Lee R M "Complications of Anticoagulant Therapy" *Surgery* 1949 XXVI 957
- Linton R R and Hardy I H Jr "Post Thrombotic Syndrome of Lower Extremity

Treatment by Interruption of Superficial Femoral Vein and Ligation and Stripping of Long and Short Saphenous Veins" *Surgery* 1948 XXIV 452

Linton R. M. Hardy I. B. Jr and Volwiler W "Portacaval Shunts in Treatment of Portal Hypertension Analysis of 15 Cases with Special Reference to Suture Type of End to Side Splenorenal Anastomosis with Splenectomy and Preservation of Kidney" *Surg Gynec & Obst* 1948 LXXXVII 129

Murray G "Anticoagulants in Venous Thrombosis and Prevention of Pulmonary Embolism" *Surg Gynec & Obst* 1947 LXXXIV 665

Nay R. M. and Barnes A. R. "Incidence of Embolic or Thrombotic Processes During the Immediate Convalescence from Acute Myocardial Infarction" *Am Heart J* 1945 XXX 65

Neuhof H *Venous Thrombosis and Pulmonary Embolism* Grune & Stratton Inc New York 1948

Ochsner A., and deBakey M. "Postphlebotic Sequelae" *JAMA* 1949 CXXXIX, 423

Ochsner A. DeBakey M. E. and DeCamp P. T. "Venous Thrombosis" *JAMA* 1950 CXLIV 831

Patterson C. O. and Rouse M. O. "Esophageal Varices" *JAMA* 1946 CXXX 384

Quick A. J. "New Concept of Venous Thrombosis" *Surg Gynec & Obst* 1950 XCI 296

Rousselot L. M. "Combined (One Stage) Splenectomy and Portacaval Shunts in Portal Hypertension With Observations on Venous Shunts in the Post Splenectomy Patients with Recurring Hemorrhage" *JAMA* 1949 CXL 282

Smith F. L., and Johnson M. A. "Incidence of Pulmonary Embolism After Venous Sclerosing Therapy" *Minnesota Med* 1948 XXXI 270

Steinhardt O. "Treatment of Obliteration of Arteries by Resection and Transplantation of Veins" *Wien klin Wchnschr* 1950 LXII 587

Thebaut, B. R. and Ward C. S. "Ligation of Inferior Vena Cava in Thromboembolism Report of 36 Cases" *Surg Gynec & Obst* 1947 LXXXIV 385

Veal J. R. and Hussey H. H. "Surgery of Deep Venous Thrombosis of the Lower Extremity" *Surgery* 1945 XVII 218

Whipple A. C. "Rationale of Portacaval Anastomosis" *Bull New York Acad Med* 1946 XXII 251

Wright I. S. "The Use of the Anticoagulants in the Treatment of Diseases of the Heart and Blood Vessels" *Ann Int Med* 1949 XXX 80



---

PART IV

DISORDERS OF CARDIOVASCULAR FUNCTION

---





---

## CHAPTER 29

---

# THE CIRCULATION OF THE BLOOD

## IMPORTANCE OF DISORDERS OF CARDIOVASCULAR FUNCTION

### CLASSIFICATION OF TACHYCARDIA, BRADYCARDIA, AND ARRHYTHMIA

---

Although William Harvey announced his discovery of the circulation of the blood over three hundred and twenty years ago (1628) it has been only within recent times that the circulation as a whole has been properly understood. The heart is but the central organ though it is to be sure the most important link in the chain. Even the blood vessels vital though they be do not complete the picture. It will be worthwhile for a moment to survey the various detailed parts of the body that share in the fascinating process of getting the blood to go where it should. Let us start with the right atrium where at its junction with the superior vena cava lies the pacemaker the *ultimum moriens* the sinoatrial node with its automatic control of the heartbeat chemically mediated by important autonomic nerves which pass on the signals from the rest of the body as to its circulatory needs with particular respect to rate. The volume and speed of the blood returning to the right atrium from all the body tissues also act reflexly to govern the action of the heart. Besides being the pacemaker the right atrium has great capacity as a storehouse to aid in preventing the overdistention of the rest of the heart furthermore the tricuspid valve as stated by King over a hundred years ago (1837) the safety valve of the heart helping to keep it from being overloaded. The pulmonary artery and its branches like the aorta by their elasticity maintain a fairly even flow of blood through the lungs instead of the forceful systolic jets both uneconomical and harmful that would be imposed on the delicate capillary structure of the pulmonary alveoli were they rigid tubes. The wonderful network of tiny vessels ramifying through the lungs not only is an ideal mechanism for exchange of gases and water between blood and alveolar air but possesses such rich anastomoses between all the larger vessels and with the bronchial cir

culation that actual blocking of one of the good sized pulmonary arterial branches is not usually followed by infarction unless there are complications of serious cardiac or pulmonary disease also the pulmonary circulation in its many ramifications can hold much extra blood if necessary without great difficulty

The act of breathing not only serves for the exchange of gases between atmospheric air and blood but it has another very important and frequently overlooked function namely to suction blood from outside the thorax into the great veins by the establishment of a negative pressure on inspiration and to drive blood forward by positive pressure on expiration This is one of the important reasons for deep breathing or other exercises to keep the diaphragm and accessory respiratory muscles fit

The great elasticity and strength of the aorta and its main branches are factors of major importance in maintaining an even and economical systemic blood flow a function often overlooked Next the arterioles should be noted an amazing autonomic mechanism for the control of the circulation in any or all parts of the body dilatation brings more blood to the organ or tissues where it is needed and keeps the blood pressure from mounting dangerously while constriction helps to divert blood from any part of the body where it is not needed to other parts which are active

The capillaries first identified by Malpighi in 1661 are the vessels for which all the rest of the structures of the circulation were originally set up In their loops there is a balancing between the hydrostatic pressure and the osmotic pressure whereby oxygen needed salts and nutritive fluids seep through to the tissues and the waste products carbon dioxide and excess fluids pass back into the capillary blood stream There is a smooth and effective gradient of blood pressure all the way from the heart or aorta itself to the venae cavae

Next the veins of the body are endowed with two mechanisms that aid greatly in the maintenance of the circulation (1) the valves which normally prevent the blood from going the wrong way and (2) the proximity of skeletal muscles which by their contractions and maintenance of good tone compress the veins and help to send blood back toward the heart Thus the important accessory aid to the circulation of blood rendered by diaphragm and skeletal muscles is reason enough to keep the whole body physically fit

An interesting and essential convenience in the circulation is the portal system actually a third subdivision of the total cardiovascular tract. Here economically food products are directly taken up and stored or utilized by the liver for the body's needs

The renal circulation carries out one of the most interesting and vital functions of the body acting as a highly selective filter of the blood to rid the body of nitrogenous waste products and excess fluid and to regulate the balance of electrolytes and water Fortunately there is a great reserve for life can continue actively for many years with but one kidney Damage by infectious toxins other bacterial invasion and metallic and other poisons

accounts for most of the kidney diseases of early life. To combat the acute renal shut-down in such cases there has been introduced in late years a most ingenious artificial kidney reference to which can be found in the Bibliography attached to this chapter. In later life vascular changes of the renal circulation account for the slowing down of renal function sometimes with acute changes but usually with a condition called chronic arteriosclerotic nephritis.

Finally the lymphatic system is a very important accessory to the circulation of blood acting to take care of all the infectious processes and foreign bodies and to perform miscellaneous tasks that cannot be readily accomplished by the cardiovascular system per se.

## DISORDERS OF CARDIOVASCULAR FUNCTION

And now last in our consideration of cardiovascular disease come disorders of circulatory function and rightly so for important and superficially impressive though they may often be they are fundamentally of less importance than the etiologic factors back of the cardiovascular disease and the structural defects that such etiologic factors leave behind them. Disorders of circulatory function fit into two groups serious disturbances often end results of severe cardiovascular disease and trivial or at any rate relatively unimportant conditions with or without such disease. Neither of these two groups should assume the major importance sometimes ascribed to disorders of function. The doctor must of course recognize and properly treat these troubles but it is far more important for him to analyze and treat so far as possible the etiologic factors behind present or future cardiovascular disease in individual or family and to search for structural defects which may some day cause serious disorders of function. Protection against heart disease and cardiovascular failure is far more vital, foresighted and profitable than the treatment of the failure itself.

Although a few disorders of circulatory function are of great importance the majority are negligible or of but slight importance. A careful analysis of functional disorders is essential therefore to differentiate the serious from the benign. The most severe disorders which are likewise of great frequency are *congestive heart (myocardial) failure*, *general vascular failure* and *coronary insufficiency causing angina pectoris* associated with myocardial failure are the grave conditions called *cardiac asthma* and *pulsus alternans*. The first two of these disorders will be discussed in the next two chapters. The third has already been discussed in Chapter 21. *Disturbances of heart rhythm* though much emphasized during the time of the development of their special study and analysis are of far less general importance than are myocardial failure and coronary insufficiency nevertheless it is necessary to recognize and to understand cardiac arrhythmia thoroughly in order to give a wise prognosis and to prescribe good treatment. Disturbances of heart rhythm include premature beats (atrial and ventricular), paroxysmal tachycardia (atrial and

ventricular), atrial fibrillation atrial flutter depression of the sinoatrial pace maker atrioventricular nodal rhythm ventricular escape (also called interference dissociation and reciprocal rhythm) atrioventricular block and intraventricular (bundle branch) block These disorders will be discussed in the three final chapters of the book Among them the only grave conditions are paroxysmal tachycardia of ventricular origin and high grade heart block both of which are rare Intelligent treatment of these and of the other disorders of heart rhythm most of which are very common affords the affected patient much relief of mind as well as of body

Circulatory failure may be subdivided in a somewhat different way from that just mentioned into the following (a) heart muscle failure secondary to specific strains such as valvular disease, hypertension and myocardial destruction which involves either left ventricle right ventricle or the whole heart (b) obstruction to the circulation with resulting congestion behind the obstruction for example congestion of the lungs from the mechanical effect of mitral stenosis and congestion of the liver from the mechanical effect of tricuspid stenosis or of acute or chronic constrictive pericarditis (c) failure of the coronary blood supply to the heart muscle (d) serious failure of cardiac rhythm due to ventricular fibrillation or cardiac standstill An interesting further subdivision of myocardial failure is into that in which there is the usual myocardial insufficiency with a decreased blood flow as in the case of hypertension or valvular disease and that in which there is increased blood flow as in the case of thyrotoxicosis beriberi arteriovenous fistula and anemia

The disturbances of normal physiology responsible for these various disorders of cardiovascular function will be taken up in each chapter under the first heading mechanism but for more detailed discussion of symptoms and signs blood pressure blood flow blood gases and graphic records the reader is referred to Part I of this book

An important part of the functional diagnosis in a cardiac patient is some sort of statement of *actual physical capacity* at the time of examination This is best expressed not by any set standards or functional tests but by the ability of the patient to carry on his routine daily activity a variable which must be considered individually for every patient A simple classification of this functional capacity is as follows

- 1 Full normal activity possible without cardiac symptoms
- 2 (a) Activity slightly restricted by symptoms  
(b) Activity moderately restricted by symptoms  
(c) Activity greatly restricted by symptoms
- 3 No activity possible without symptoms
- 4 Symptoms even at rest

Thus a complete cardiovascular diagnosis should include four features first etiology second structural change third disorders of function and fourth physical capacity The following are examples of complete diagnoses

Rheumatic heart disease with mitral stenosis atrial fibrillation and congestive failure activity greatly restricted by symptoms

Congenital cardiovascular disease with patency of the ductus arteriosus full normal activity possible without symptoms

Syphilitic aortitis with aortic regurgitation and angina pectoris symptoms even at rest

Hypertensive heart disease with activity slightly restricted by dyspnea

Although a large part of the treatment of functional circulatory disorders must be symptomatic it is equally important as I have suggested a few paragraphs earlier to treat the underlying diseases when possible and especially to try to practise preventive medicine. Fortunately more attention is being paid at the present time than formerly to the prevention of disease and when disease is already present to the prevention so far as is possible of the further progress of that disease and of the failure of function. Such measures are especially applicable to diseases of the heart. Not only must we try to abolish conditions which cause structural abnormalities of the heart but we must attempt in the presence of such abnormalities to keep strain from inducing functional disorders. Here the occupational training and placement of cardiac patients is of great importance. Sound judgment of all the factors involved—training mental ability physical capacity family responsibility opportunities happiness and preferences of every individual patient—must decide the matter of work for each case rather than any set of rules or standards no matter how elastic. Many measures such as attendance at health resort sanitarium and spa are far more fruitful when used in a prophylactic way than when used in therapy. Sound advice which is heeded is worth an immeasurable amount of medicine and the wise and careful regulation of living almost always adds to the duration of life to its fullness and to its accomplishments whether slight or serious heart disease be present.

In this introductory chapter it will be of value to consider the disorders of the heartbeat from the standpoint of general classification according to rate and rhythm to supplement their individual consideration in later chapters. The following tabulation gives the various types and causes of tachycardia bradycardia and arrhythmia. The terminology employed throughout the book has been changed in accordance with the new international nomenclature to atrial and atrio instead of auricular and auriculo.

## TACHYCARDIA

Tachycardia (*ταχὺς* quick and *καρδία* heart)

1 Sinoatrial tachycardia. This consists of regular rapid heart action as a rule at rates in the adult between 80 and 160 per minute with gradual onset and offset and is generally due to the combined effect on the sinoatrial node of depression of vagal action and of stimulation of sympathetic nerve action and less often to either effect alone. Rarely the rate may rise above 160 even

to 200 or more. The normal heart rate of the young infant varies from 100 to 150 at rest and of the child below adolescence from 80 to 120 though there are frequent exceptions with slower rates.

The causes of tachycardia are

a Normal mechanism in some healthy individuals (but not over the rate of 100 in adults at complete rest)

b Physiologic reaction to exertion ingestion of food excitement and pain

■ Voluntary acceleration Rare. Due primarily to unusual sympathetic nerve control and attended by increase of blood pressure and by pupillary dilatation. The heart rate may be doubled as from 80 to 160. The acceleration is rapid requiring a few beats to full speed and not instantaneous. It is still possible even after paralysis of the vagi by atropine (Favill and White 1917).

d Neurocirculatory asthenia some cases in part probably due to effort of heart to compensate for a relatively small venous blood return to the heart and in part due to apprehension.

e Reaction to other factors that reduce considerably the amount of blood returned to the heart these factors include vasomotor shock hemorrhage long standing in the erect position without movement pooling of blood in extensive varicose veins and acute and chronic constrictive pericarditis.

f Reaction to certain substances such as coffee tea and tobacco and to certain drugs such as epinephrine (adrenaline) via sympathetic nerve stimulation.

g Reaction to drugs such as atropine causing decrease in vagal action and to diseases like diphtheria and poliomyelitis which may cause vagal paralysis.

h Thyrotoxicosis

i Reaction to toxins of infections. With every degree of fever there is an acceleration of approximately ten heartbeats per minute.

j Reaction to pulmonary embolism

k Reaction to heart disease and failure itself

2 Paroxysmal tachycardia. This consists of a regular rhythm at heart rates usually of 120 to 320 per minute averaging 160 with sudden onset and offset. The fastest rates are found in young infants. The duration of paroxysms varies from a few seconds to several days but is usually a few minutes to a few hours.

The causes of paroxysmal tachycardia are primarily abnormal irritability of the heart and secondarily various exciting factors. Heart disease itself is not the usual cause. Complete discussion of this disturbance of cardiac rhythm will be found in Chapter 32. The types of paroxysmal tachycardia are

a Atrial. Usually ectopic rarely at or very near the sinoatrial node. As a rule unimportant but annoying.

b Ventricular. Rare. Usually serious.

■ Atrioventricular nodal. Very rare. Not serious.

3 Atrial flutter. This consists of a regular or regularly irregular rhythm at atrial rates usually of 200 to 400 averaging 300 and ventricular rates

usually at one half the atrial rates due to 2 to 1 heart block. The onset is sudden. The duration of atrial flutter varies from a few hours to several years but is usually a few days or weeks. The causes of atrial flutter are as in the case of paroxysmal tachycardia: abnormal irritability of the heart and various exciting factors, heart disease is usually present. Atrial flutter will be discussed fully in Chapter 33.

4 **Atrial fibrillation** This consists of absolute arrhythmia at atrial rates of 300 to 500 per minute, averaging 400, and ventricular rates at about 150 before treatment. Its onset is sudden. It is usually permanent but in about one fourth of the cases paroxysmal, the paroxysms lasting several hours each. Heart disease is usually present in this disturbance of rhythm but sometimes the condition is wholly functional. Full discussion will be found in Chapter 33.

### BRADYCARDIA

Bradycardia (*βραδύς* slow and *καρδιά* a heart)

1 **Sinoatrial** This is due chiefly to preponderance of vagal action on the sinoatrial node. The rhythm is regular or irregular (sinus arrhythmia) at heart rates of 30 to 60, usually about 45. The causes are

- a Normal mechanism in some individuals even at a heart rate in the 30s in a few distance runners at rest
- b Physiologic reaction to rest, sleep, vagal stimulation by carotid sinus pressure in the neck or by ocular pressure and sometimes to cold and fright
- c An occasional reaction to convalescence from certain infectious diseases for example influenza especially in youth and often after childbirth
- d Reaction to increased intracranial pressure (hemorrhage, tumors, meningitis)

e Reaction to certain diseases: hepatitis with jaundice, mumps

f Reaction to drugs especially digitalis

2 **Atrioventricular nodal rhythm**, a very rare mechanism, consists of a regular heart beat at about 40 per minute; the atrioventricular node controlling both atria and ventricles. It is a relatively unimportant functional disorder of unknown cause to be discussed in Chapter 34.

3 **Atrioventricular block** This consists of a regular or irregular rhythm usually regular (due to 2 to 1 or to complete block) less often irregular (due to frequent dropped beats or to varying grades of block especially 3 to 2). The atrial rate is usually normal and the ventricular rate 20 to 60, being about 40 to 50 with partial block and 30 to 40 with complete block. It is usually of organic origin. Full discussion will be found in Chapter 34.

### ARRHYTHMIA

Arrhythmia (*α* privative not and *ρυθμός* measured motion)

1 **Sinus arrhythmia** presents a heart rate usually varying with phases of respiration but sometimes very irregular. It is a functional condition only. The



heart may be diseased but usually it is not. Further discussion will be found in Chapter 34.

2 **Premature beats (extrasystoles)** may be few or many in number producing a regular irregularity as a rule. They are more frequently found with slow than with fast pulse rates and without than with heart disease. They are caused by excessive irritability of the heart by exciting extracardiac factors or by both. Full discussion will be found in Chapter 32. There are several types of premature beats as follows:

- a Atrial. Not followed by compensatory pause. Occasional.
- b Ventricular. Usually followed by compensatory pause. Common.
- c Atrioventricular. There is no compensatory pause if the premature beat controls both atria and ventricles, but there is a compensatory pause if the premature beat is only an escape of the ventricle. Rare.

3 <b>Atrial flutter.</b> There is cardiac arrhythmia in only about half the cases of atrial flutter and when the arrhythmia occurs it is usually a regular irregularity.	} See above under Tachycardia and Bradycardia for other observations concerning these disorders of rhythm.
4 <b>Atrial fibrillation.</b> Absolute arrhythmia.	
5 <b>Atrioventricular block.</b> The ventricular rhythm is often irregular in partial block but rarely irregular in complete block.	

### RELATIVE FREQUENCY OF DISORDERS OF HEART RHYTHM

To illustrate the relative frequency of the various disorders of the heartbeat shown *electrocardiographically* among individuals who consult medical advice because of cardiovascular symptoms or signs, I am adding herewith the findings in the order of frequency among 10 000 patients electrocardiographed at the Massachusetts General Hospital in the sixteen years from 1914 to 1931: atrial fibrillation 1 422 cases (14.22 per cent); ventricular premature beats 974; partial atrioventricular block (including 296 cases with long P-R intervals without dropped beats) 562; intraventricular block of lesser degrees 511; atrial premature beats 512; bundle branch block 223; atrial flutter 104; atrial paroxysmal tachycardia 80; complete atrioventricular block 79; sinoatrial block (including 18 cases of atrial standstill) 61; atrioventricular nodal premature beats 17; ventricular paroxysmal tachycardia 14; atrioventricular nodal rhythm 14; and atrioventricular nodal paroxysmal tachycardia 4 (0.04 per cent) (White and Sprague, 1931).

A more recent review of the index files of the electrocardiograms of the Massachusetts General Hospital covering the nine years from February 1934 to January 1943, including 25 000 patients, has shown a different incidence of disorders of cardiac rhythm, doubtless due in part to the more routine use of this method of study. Hence the new figures are a somewhat better indication of the true incidence of these disorders. Ventricular premature beats led the list, being found in 2 007 cases; atrial fibrillation was second with 1 620 cases; partial a-v block third with 1 135 cases; full bundle branch block

fourth with 1 040 cases atrial premature beats fifth with 984 cases and then in order intraventricular block of lesser grades (363 cases) atrial paroxysmal tachycardia (151 cases) atrial flutter (139 cases) complete a v block (104 cases) ■ a block (65 cases) ■ v nodal premature beats (43 cases) ventricular paroxysmal tachycardia (36 cases) a v nodal rhythm (32 cases) and ■ v nodal paroxysmal tachycardia (15 cases) (analyzed with the kind help of Louise Wheeler)

The relative frequency of the various disorders of the heartbeat actually experienced by patients is not fairly represented by the data obtained from the analysis of electrocardiograms since transient arrhythmias chiefly in the form of premature beats or extrasystoles are frequently missed in the short records usually taken. It is quite certain from clinical analysis that ventricular premature beats are several times probably many times more common than atrial fibrillation which happened in the first series of cases noted above to be the commonest disorder found electrocardiographically also for the same reason paroxysmal atrial tachycardia is undoubtedly much more common than the figures given here suggest

## BIBLIOGRAPHY

### DISORDERS OF CARDIOVASCULAR FUNCTION

#### (INCLUDING CERTAIN PHYSIOLOGIC AND ANATOMIC OBSERVATIONS)

- Anatomic and Physiologic References (See also General References and references under Chapters 3 6 8 9 10 21 24 25 and 34 )
- Abramson D I and Jochim K 'The Spread of the Impulse in the Mammalian Ventricle' *Am J Physiol* 1937 CXX 635
- Alexander H L 'The Autonomic Control of the Heart Lungs and Bronchi' *Ann Int Med* 1933 VI 1033
- Anrep G V and Segall H N 'The Regulation of the Coronary Circulation' *Heart* 1926 XIII 239
- Braeucker W 'Der Brustteil des vegetativen Nervensystems und seine klinischchirurgische Bedeutung' *Beitr z Klin d Tuberkulose* 1927 LXVI 1
- Burstein C L and Rovenstone E A 'Circulatory Disturbances Reflexly Inaugurated by Stimulation of Celiac Plexus' *Arch Surg* 1937 XXXV 599
- Cannon W II and Bacq Z M 'Studies on the Conditions of Activity in Endocrine Glands XXVI A Hormone Produced by Sympathetic Action on Smooth Muscle' *Am J Physiol* 1931 XCVI 392
- Cannon W II Lewis J T and Britton S W 'Studies on the Conditions of Activity in Endocrine Glands XVII A Lasting Preparation of the Denervated Heart for Detecting Internal Secretion with Evidence of Accessory Accelerator Fibers from the Thoracic Sympathetic Chain' *Am J Physiol* 1926 LXXVII 3-6
- Cannon W II and Rosenbluth A *Autonomic Neuro Effector Systems* Macmillan Co New York 1937
- Drinker C K 'The Formation and Movements of Lymph' *Am Heart J* 1939 XVIII 389
- Favill J and White P D 'Voluntary Acceleration of the Rate of the Heart Beat' *Heart* 1917 VI 175
- Gaskell W A 'On the Innervation of the Heart with Especial Reference to the Heart of the Tortoise' *J Physiol* 1882 IV 43
- Gasser H S and Meek W J 'A Study of the Mechanisms by Which Muscular Exercise Produces Acceleration of the Heart' *Am J Physiol* 1914 XXXIV 48

- Haddad E I and Khairallah A A A Forgotten Chapter in the History of the Circulation of the Blood *Ann Surg* 1936 CIV 1
- Harvey William *Exercitatio anatomica de motu cordis et sanguinis in animalibus* Guiljelmi Fitzeri Francofurti 1628 (The first English text of 1653 has been newly edited by Geoffrey Keynes 1928 Nonesuch Press London)
- Henderson Y The Volume Curve of the Ventricles of the Mammalian Heart, and the Significance of This Curve in Respect to the Mechanisms of the Heart Beat and the Filling of the Ventricles *Am J Physiol* 1906 XVI 325
- Henderson Y Oughterson A W Greenberg L A and Searle C P The Third Major Mechanical Factor in the Circulation of the Blood *Science* 1934 LXXIX 508
- Heymans C The Pressoreceptive Mechanism for the Regulation of Heart Rate Vasomotor Tone Blood Pressure and Blood Supply *New England J Med* 1938 CCXIX 147
- His W Jr "Die Thätigkeit des embryonalen Herzens und deren Bedeutung für die Lehre von der Herzbewegung beim Erwachsenen *Arbeiten aus der med Klin* Leipzig 1893 p 14
- Hunt R Direct and Reflex Acceleration of the Mammalian Heart with Some Observations on the Relations of the Inhibitory and Accelerator Nerves" *Am J Physiol* 1899 II 395
- Keith A and Flack M The Form and Nature of the Muscular Connections between the Primary Divisions of the Vertebrate Heart *J Anat and Physiol* 1907 XLI 172
- Kent A F Researches on the Structure and Function of the Mammalian Heart *J Physiol* 1893 XIV 233
- King T W The Safety Valve Function in the Right Ventricle of the Human Heart. *Guys Hosp Rep* 1837 II 132
- Kuntz A The Autonomic Nervous System Essential Anatomy *JAMA* 1936 CVI 345
- Levine H B and White P H What Sensible Living and Natural Recovery Can Do for a Cardiac Patient *New England J Med* 1941 CCXXV, 101
- Lewis T The Law of Cardiac Muscle with Special Reference to Conduction in the Mammalian Heart *Quart J Med* 1921 XIV 339
- Malpighi M *De pulmonibus observationes anatomicae* Bologna 1661
- Newton H F Zwemer H L and Cannon W B Studies on the Conditions of Activity in Endocrine Glands XXV The Mystery of Emotional Acceleration of the Denervated Heart After the Exclusion of Known Humeral Accelerators" *Am J Physiol* 1931 XCVI 377
- Purkinje J E "Mikroskopisch neurologische Beobachtungen *Arch f Anat Physiol u wiss Med* 1845 p 281
- Sanderson J B and Page F J M On the Time Relations of the Excitatory Process in the Ventricle of the Heart of the Frog *J Physiol* 1880 II 385
- Stannius H "Zwei Reihen physiologischer Versuche *Arch f Anat Physiol u wiss Med* 1852 p 83
- Starling E H *Principles of Human Physiology* Lea & Febiger Philadelphia 4th ed 1930 (1st ed 1912) Edited and revised by C Lovatt Evans and H Hartridge
- Tandler J *Anatomie des Herzens* Gustav Fischer Jena 1913
- Tarchanoff J R Ueber die willkürliche Acceleration der Herzschläge beim Menschen *Pflügers Arch f d ges Physiol* 1884 XXXV 109
- Tawara S *Das Reizleitungssystem des Säugetierherzens* Jena 1906
- Wenckebach K F *Her- und Kreislaufinsuffizien* Th Steinkopff Dresden and Leipzig 1931
- White J C Garrey W E and Atkins J A "Cardiac Innervation Experimental and Clinical Studies" *Arch Surg* 1933 XXVI 765
- Wiggers C J *Modern Aspects of the Circulation in Health and Disease* Lea & Febiger Philadelphia 3rd ed revised 1939 (1st ed 1915)
- Recent References (1944-1950)*
- Brull L "A Mechanical Heart with Coagulable Blood" *Science* 1950 CXI 277
- Chapman F M Kinsey B Chapman W P and Smithwick R H Sympathetic Innervation of the Heart in Man Preliminary Observations of the Effect of Thoracic Sympathectomy on Heart Rate" *JAMA* 1948 CXXXVII 579

- Feil H Green H D and Eiber D "Voluntary Acceleration of Heart in a Subject Showing the Wolff Parkinson White Syndrome" *Am Heart J* 1947 XXXIV 334
- Jongbloed, J "Mechanical Heart Lung System" *Surg Gynec & Obst* 1949 LXXIX, 684
- Merrill J P Thorn G W Callahan E J and Smith S "Clinical Experience with the Use of an Artificial Kidney" *J Clin Investigation* 1949 XXVIII 798
- Robb J S "A Study of the Detail of Muscle Insertions in the Heart" *Bull Internat A M Museums* 1949 XXX 84
- Robb J S Kaylor C T and Turman W G "A Study of Specialized Heart Tissue at Various Stages of Development of the Human Fetal Heart" *Am J Med* 1948 V 374
- Selye H "The General Adaptation Syndrome and the Diseases of Adaptation" *J Clin Endocrinol* 1946 VI 117
- Trueta J., et al *Studies of the Renal Circulation* Charles C Thomas Springfield IL 1947
- Arrhythmia (For other references see Chapters 32 Premature Beats 33 Atrial Fibrillation and Flutter and 34 Heart Block)**
- Battro A *Las Arritmias en Clinica Diagnostico Pronostico y Tratamiento* El Ateneo Buenos Aires 1948
- Clerc A *Les arhythmies en clinique* Masson et Cie Paris 1925
- Crittendon P J and Ivy A C "A Study of Viscerocardiac Reflexes I The Experimental Production of Cardiac Irregularities by Visceral Stimulation" *Am Heart J* 1933 VIII 496
- Lewis T *The Mechanism and Graphic Registration of the Heart Beat* Shaw and Sons Ltd London 3rd ed 1925 (1st ed 1911)
- Clinical Disorders of the Heart Beat* Shaw and Sons Ltd London 7th ed 1933 (1st ed 1912)
- Landtman B "Heart Arrhythmias in Children" *Acta Paediatrica* 1947 XXXIV Suppl I
- Linenthal A J and Freedberg A S "Medical Progress Measures Used in the Prevention and Treatment of Cardiac Arrhythmias" *New England J Med* 1949 CCXLI 570 and 612
- Mackenzie J *Diseases of the Heart* Henry Froude Hodder and Stoughton Oxford University Press 3rd ed 1913 (1st ed 1908)
- Matthews E and Wood W B Jr "Cardiac Arrhythmia During Cheyne Stokes Respiration" *Bull Johns Hopkins Hosp* 1940 LXVI 335
- Perez de los Reyes R and de la Torre H "Arritmias de la Infancia" *Revista Cubana de Cardiol* 1947 VIII 145
- Wenckebach K F and Winterberg H *Die unregelmässige Herzthätigkeit* W Engelmann Leipzig 1927
- Wesolowski M A Miller H H Halkett J A E and Welch C S "Experimental Replacement of the Heart by a Mechanical Extracorporeal Pump" *Bull New England Med Center* 1950 XII 41
- White P D and Sprague H B "Electrocardiography of 10 000 Patients at the Massachusetts General Hospital from 1914 to 1931" *Kasan M J (USSR)* 1931 p 381

# MYOCARDIAL INSUFFICIENCY (CONGESTIVE HEART FAILURE) DIGITALIS THERAPY DIURETIC DRUGS

---

Even though heart muscle failure is usually a late and often the final event in the course of heart disease and so of less fundamental importance than the earlier stages and especially in comparison with preventive measures it is nevertheless a very serious condition demanding early recognition and adequate treatment. Fortunately although there still remain obscurities about its pathogenesis there have been important advances both in the understanding of its mechanism and especially in its treatment since the last edition of this book.

Myocardial insufficiency giving rise to congestive heart failure is the commonest of the important functional disorders of the heart. It develops eventually and often terminally in more than half of all individuals with organic heart disease. It also occurs in a few individuals without organic heart disease but with sudden abnormal strain as in the case of massive pulmonary embolism or of prolonged and extreme paroxysmal tachycardia in infancy.

An unsatisfactory designation for severe congestive heart failure once customary in France but now being discarded was *asystolie*—this means literally cardiac standstill which would quickly precipitate death.

**Mechanism (abnormal physiology)** Under the effect of strain of various kinds the heart muscle may be unable to maintain a satisfactory circulation, so that vascular stasis in various parts of the body results. Such stasis when it produces symptoms or signs is called congestive failure but the myocardium often weakens long before gross signs of congestion appear and various body structures and tissues such as the kidneys and the brain may suffer from a resulting lack of adequate circulation. Myocardial failure may come suddenly or slowly. The strain is for the most part unilateral at first and one ventricle begins to fail before the other or when both ventricles fail together the weakness of one may be preponderant. Moreover failure of the left ventricle soon adversely affects the right ventricle.

Failure of the myocardium has a twofold deleterious effect consisting of inadequate blood supply distal to the ventricle involved (*forward failure*)

and of congestion or stasis proximal to it or behind it For many years there has been much controversy as to these effects but now it is generally agreed that both points of view should be accepted and that myocardial failure acts in both ways

*Failure of the left ventricle* is the commonest type of heart failure It may be acute as from massive myocardial infarction or sudden tachycardia superimposed on chronic left ventricular strain or it may be gradual in its development from hypertension or aortic valve disease When left ventricular failure results from the constant severe strain of chronic hypertension dilatation occurs in the already hypertrophied left ventricle which is no longer able to pump on all the blood it receives from the right ventricle the mitral valve may or may not become relatively insufficient the left atrium is overfilled the lung vessels are engorged the pulmonary arterial pressure becomes greatly increased and the right ventricle unaccustomed to work against such high pressure which in some cases equals or even exceeds that in the systemic circulation must increase its activity to make up for the added burden thrown upon it In such a case if the sequence of events is slow in development the right ventricle in its turn becomes hypertrophied and eventually dilates and fails along with the left ventricle Death may come however before the strain on the right ventricle has progressed so far or even before any right ventricular hypertrophy has had time to develop The significant effect on the lungs of left ventricular failure was pointed out over a hundred years ago particularly by Hope (1832)

Hope J *A Treatise on the Diseases of the Heart and Great Vessels* William Kidd London 1832

Page 196 'As an obstacle to the circulation operates on the heart in a retrograde direction the cavity immediately behind it is the first to suffer from its influence Accordingly all the impediments seated in the aorta its mouth or the arterial system act primarily on the left ventricle which being likewise exposed to the heaviest burden when the circulation is accelerated has to conflict against a greater variety of exciting causes of hypertrophy than any other cavity of the heart On this account therefore as well as from the thickness of its parietes it is subject to hypertrophy in a greater degree than any other

So long as the left ventricle is capable of propelling its contents the corresponding auricle being protected by its valve remains secure Hence in a great majority of cases the auricle is perfectly exempt from disease while the ventricle is even enormously thickened and dilated But when the distending pressure of the blood preponderates over the power of the ventricle its contents from not being duly expelled constitute an obstacle to the transmission of the auricular blood Hence the auricle becomes over distended and the obstruction may be propagated backwards through the lungs to the right side of the heart and there occasion the series of phenomena

Page 205 'The primary effect of universal obstruction of the lungs by engorgement is to produce œdema of their cellular tissue and dyspnoea whether the latter depends solely on the engorgement or partly also on spasm of the bronchi excited by the irritation of that congestion is difficult positively to determine

though the latter is highly probable To this subject I shall revert hereafter The secondary effect is to gorge the right side of the heart and thus impede the return of the venous blood from the system at large which co operates with the increased energy of the arterial circulation in producing anasarca

*Failure of the right ventricle* may be more responsible in some cases for symptoms signs and even for death itself than the left ventricular failure that usually comes first If the right ventricle fails because of the strain of left ventricular failure or of chronic mitral stenosis or extensive pulmonary fibrosis it is not able to pass on all the blood it receives through the lungs to the left side of the heart it becomes dilated the tricuspid valve may be insufficient the right atrium is engorged and the blood flow in the coronary sinus the great and small veins and capillaries is hampered and often greatly slowed Dropsy or anasarca with dependent edema ascites and hydrothorax is the end stage of right ventricular failure Engorgement of the neck veins was well described as a special sign of dilatation of the right ventricle over 200 years ago by Lancisi (1728)

Lancisi J M *De Motu Cordis et Aneurysmatibus* J M Salvioni Rome 1728  
page 141 (Translation by myself)

Dilatation of the right auricle and ventricle leads to two consequences worthy of the greatest consideration and these in turn lead to periodic dilatation of the jugular veins The first consequence is extreme dilatation of the venæ cavae in which the blood may remain for a long time in copious amount Secondly the orifice of the root of the vena cava is so enlarged that the [tricuspid] valve cusps no longer close Hence it happens that with contraction of the heart blood is expelled from the right ventricle not only into the lungs through the pulmonary artery but also into the wide open superior vena cava by way of the right auricle and thence into the jugulars

Occasionally the heart fails in toto when both ventricles are affected by some common strain such as severe rheumatic carditis or severe anemia Then both ventricles dilate with resulting congestion in both the pulmonary circulation and the systemic veins the atrioventricular valves may become insufficient

Certainly the most obvious evidence of advancing weakness of either ventricle is congestion behind that ventricle in the lungs in the case of the left ventricle and in the great veins and liver in the case of the right A decrease in the power of the circulation in front of the weakened ventricle undoubtedly commonly occurs too but is much less evident clinically except under certain circumstances as in the case of the cerebral and coronary circulation in the presence of marked aortic stenosis and failure of the left ventricle and in the case of inadequate renal function on occasion when the blood pressure falls as the result of weakening of a hypertensive left ventricle even before congestion develops The most striking instance of forward failure of the circulation as a whole is that occurring in vascular collapse with resulting inadequate amount of blood reaching and leaving the heart rare cases of

extremely rapid heart rates in paroxysmal tachycardia and flutter also belong there (see Chapter 32)

Failure of the left ventricle occurs as a primary manifestation of myocardial insufficiency at least three times more often than does failure of the right ventricle. That this should be so is evident when we compare the relative frequency of the factors (hypertension, aortic valve disease and myocardial infarction) responsible for left ventricular strain with those (mitral stenosis and pulmonary fibrosis) responsible for primary right ventricular strain (White 1933 and 1942, Boyer, Leach and White 1940) that it actually is so is indicated by the far greater incidence of dyspnea in early heart failure than of engorgement of neck veins and liver.

The precise way in which the heart muscle under strain dilates and fails is not wholly clear but the fundamental factor is doubtless a chemical one. An excessive content of lactic acid in muscle results from excessive work and is associated with fatigue. Redfield and Medearis (1926) have shown that the ability of the ventricular muscle of the turtle to develop tension is closely correlated with its content of lactic acid—the more the lactic acid the less the tension possible.

In the discussion in Chapter 25 on cardiac hypertrophy and dilatation it has already been pointed out that hypertrophy is probably a reaction to abnormal stretching or dilatation of the muscle fibers but from the clinical point of view except in the occasional cases of acute dilatation of the heart hypertrophy of either ventricle or of both often progresses very slowly and precedes evident dilatation and failure by a considerable length of time even by many years such hypertrophy at its onset may not be evident on examination.

The three important changes that have come in the point of view concerning cardiac dilatation and failure in the last generation of medical literature in the English language go back to some of the viewpoints of long ago swept aside by too hasty an interpretation of various findings in our own time. These three changes are as follows: (1) the heart is not functionally or even anatomically one organ when it is concerned with strains on any individual chamber since a single ventricle may enlarge greatly without immediate effect on the rest of the heart even though the muscle bands are continuous throughout the heart and since that ventricle may itself alone fail under strain, (2) heart failure shows itself most prominently by the presence of congestion behind the weakened chamber and not so clearly ahead of it (that is distally) although there is considerable truth in the points of view of both those who have supported the back pressure theory and those who hold the forward failure thesis—neither one alone tells the whole story and (3) there is such a thing as acute dilatation of either ventricle or of both although chronic gradual failure is more the rule.

Atrial failure and dilatation are of far less importance than are ventricular failure and dilatation but they have sometimes a certain amount of significance as discussed in the chapters on cardiac enlargement and atrial fibrillation.



**Etiology Cause** Almost any kind of heart strain can eventually cause congestive heart failure but certain factors are much more important or common than others and very often several factors are combined to precipitate failure in the same case. The commonest causes of congestive heart failure are valvular defects (mitral and aortic) chronic hypertension and myocardial infarction from coronary thrombosis. Less common but still very important are severe rheumatic carditis thyrotoxicosis extensive pulmonary fibrosis congenital defects anemia and abnormally fast heart rates as in long continued and uncontrolled atrial flutter atrial fibrillation and paroxysmal tachycardia. Rare causes are arteriovenous aneurysm cardiac trauma thoracic deformities external pericardial adhesions and tumors. Left ventricular failure is as stated above much more commonly initial than is right ventricular failure because the left ventricle is more often subject to strain particularly as the result of hypertension narrowing or occlusion of the descending branch of the left coronary artery and aortic stenosis or regurgitation. Special strains affecting directly the right ventricle are also of great importance left ventricular failure (by far the most common of all) mitral stenosis chronic pulmonary disease including emphysema and congenital pulmonary stenosis. It has been suggested that bulging of an hypertrophied and dilated left ventricle via the septum into the right ventricle may be an important factor in obstructing the flow of blood through the right ventricle and so favoring the occurrence of systemic venous congestion (the so-called Bernheim's syndrome 1910), it is doubtful however, how important this is since the increased pulmonary pressure due to left ventricular failure unquestionably plays a much larger role since the right ventricle can quite readily adapt itself to changes in shape and size of the left and since pulmonary complications including embolism commonly occur in left ventricular strain and weakness and may be easily overlooked (Kinsey and White 1940).

Certain conditions act on both ventricles more or less equally such as rheumatic carditis anemia the abnormal tachycardias (atrial fibrillation atrial flutter and paroxysmal tachycardia) thyrotoxicosis generalized coronary narrowing mitral regurgitation and certain congenital defects like patency of the ductus arteriosus. Special atrial strain comes with stenosis and regurgitation of mitral and tricuspid valves with ventricular dilatation and with certain congenital defects especially interatrial septal defects.

In a person with heart disease failure is often precipitated by a relatively trivial circumstance such as a slight respiratory infection overeating excitement or slight overexertion but usually heart failure is of gradual onset without any particular precipitating factor. In children acute rheumatic infection is the most frequent immediate cause.

It is of considerable interest and value to differentiate the underlying and exciting causes of congestive heart failure. An analysis of 1 000 cases (Boxer Lerch and White 1940) has shown the following fundamental and precipitating factors. The former were hypertension 46.9 per cent (21.3 without and 25.6 with coronary heart disease) coronary disease 41.4 per cent (15.8 with

out and 25.6 with hypertension) rheumatic heart disease 25.7 per cent syphilitic 3.0 per cent cor pulmonale 2.5 per cent calcareous aortic stenosis 1.0 per cent congenital defects 0.7 per cent and miscellaneous and unknown 2.57 per cent. The precipitating factors were atrial fibrillation 14.0 per cent coronary thrombosis 12.8 per cent respiratory infection 10.5 per cent rheumatic fever 6.0 per cent pulmonary embolism 3.3 per cent other infections 1.9 per cent malignant hypertension 1.7 per cent exertion 1.4 per cent anemia 1.0 per cent thyrotoxicosis 0.7 per cent surgical operations 0.5 per cent paroxysmal tachycardia 0.4 per cent indigestion or gallbladder colic 0.3 per cent cough 0.2 per cent pregnancy 0.2 per cent asthmatic attack 0.2 per cent trauma 0.2 per cent excessive fluid intake 0.1 per cent emotion 0.1 per cent and unknown 43.9 per cent (acting suddenly in 4.8 per cent and gradually in the rest). Thus hypertension coronary heart disease and rheumatic heart disease are in the order named by far the most common fundamental causes of heart strain and failure in New England today. The most common recognizable precipitating factors are first the tachycardia of atrial fibrillation second infarction of heart or lungs and third various infections in particular respiratory and rheumatic however, a large percentage of cases fail gradually without evident precipitating factor and these have the poorest prognosis.

**Sex.** Both sexes are equally subject to congestive heart failure but it occurs earlier and more severely as a rule in males. Cyclical premenstrual congestion may be the first evidence of heart failure in the female.

**Age.** Congestive heart failure is found more often in old than in young persons three fourths of all the cases being more than fifty years old. Nevertheless it is seen at all ages even in childhood when it is sometimes precipitated by a severe rheumatic pancarditis which interestingly enough affects the entire heart or at any rate the right ventricle so severely that the signs of the congestive failure are almost wholly limited to the systemic and portal circulations (increased venous pressure generalized edema engorged liver) while the lungs remain free (Walsh and Sprague 1941).

**Pathology.** There are no lesions characteristic of congestive heart failure. It is a functional condition which is almost invariably associated with organic heart disease. A perfectly normal heart may however fail if it is under sufficient strain in such cases it is a question purely of muscle fatigue with the abnormal chemical state that exists in an exhausted muscle. Much has been written about abnormality and limited reserve of the myocardium as the primary causes of heart failure while such factors as valvular disease have been considered more or less incidental this point of view is only partially correct. In fact the older views that certain organic lesions were of prime importance were more nearly right than the recent teaching that the heart muscle is everything and that little else matters. It is of great importance to realize that a heart muscle strong and even massive and healthy may fail simply from severe strain in its effort to overcome some defect without sign of any degeneration or inflammation as is frequently illustrated by the hypertrophied healthy

ventricular muscle in a heart that has failed from essential hypertension (hypertrophia) and by the hypertrophied healthy right ventricular muscle in a heart that has failed from marked mitral stenosis. It is this truth that has not been sufficiently emphasized in the recent past. But it is also true that the heart may fail without structural defects or hypertension when there is some direct deleterious effect on the myocardium as in a severe rheumatic infection or in severe anemia. Such direct myocardial effects are frequently superimposed on chronic structural lesions.

The commonest structural abnormality found with congestive heart failure is cardiac enlargement consisting usually of both hypertrophy and dilatation and rarely of dilatation alone. Dilatation without hypertrophy is found when the failure has been acute and rapid as with coronary thrombosis or fulminating rheumatic carditis or prolonged extreme paroxysmal tachycardia. Either ventricle may be primarily affected; in the long-continued chronic cases both ventricles are involved. It is of more than passing interest that by far the most common cause of enlargement of the right ventricle (beginning as hypertrophy) is chronic failure of the left ventricle and not mitral stenosis or severe chronic pulmonary disease or other factor (Thompson and White 1936). Frequently the atria are also enlarged in heart failure. The myocardium shows an increased content of water in anasarca from congestive heart failure (Gross 1940). Valvular disease, especially aortic regurgitation or mitral stenosis, is occasionally present. Coronary arterial narrowing is sometimes found particularly in well marked cases when occlusion of the descending branch of the left coronary artery causes dilatation and failure of the left ventricle. An adherent pericardium and congenital defects are much less commonly seen but they do occur in some cases. Generalized arteriosclerosis and aortic aneurysm often accompany congestive heart failure but they are apparently merely incidental. Sclerosis of the superior vena cava has been noted as a sequel of long-continued elevation of venous pressure in chronic congestive heart failure (Gross and Handler 1939).

Summarizing the result of a postmortem study of 102 cases of myocardial failure Clawson in 1924 wrote: Coronary sclerosis of serious degree was present in 22.5 per cent. Myocardial fibrosis was found in a marked or moderate degree in 20.5 per cent and in a slight degree in 30 per cent. There is usually a close correspondence between the situation and the extent of myocardial fibrosis and the distribution and degree of the coronary sclerosis. Myocardial fibrosis is usually due to coronary disease but occasionally rheumatic infections may give rise to a slight degree of fibrosis. Myocardial strain (hypertensive or nonhypertensive) is not a cause of myocardial fibrosis. Syphilitic myocarditis is rare. Myocardial failure is rarely due to anatomical changes in the myocardium. It may be explained as an exhaustion of the cardiac muscle. True chronic inflammation of the myocardium is very rare. What is commonly called chronic myocarditis is usually myocardial fatigue resulting from the various conditions mentioned above. Approximately half of the cases of myocardial failure show no anatomical changes in the heart muscle. The anatomical

ical changes in the heart muscle are seldom sufficient in themselves to cause death. With these statements I agree.

The pathologic effect of congestive heart failure on other organs and tissues of the body is by the production of edema, mostly interstitial in its site (even in the lungs). If very long-continued edema may result in actual tissue change, especially in the liver, but Sherlock (1951) has shown by biopsy that the liver may regenerate after damage (centrilobular hepatic necrosis) resulting from severe congestion, when there is improvement in the circulation.

**Symptoms.** Since left ventricular strain is far more common than right or biventricular strain, the earliest and chief symptom of congestive heart failure is usually *dyspnea* at rest or on effort not previously causing breathlessness. Such dyspnea is due primarily to any one or more of several factors, most commonly a reflex stimulating the respiratory center and arising in the lungs from congestion of the pulmonary circulation, also the effect of oxygen lack (anoxemia) on the respiratory center, and a central reflex arising from acute or subacute distention of the atria and great veins. Cardiac dyspnea from the first mentioned and most common factor, namely the pulmonary reflex, which results from failure of the left ventricle and not of the right, must be differentiated from other causes of dyspnea giving rise to such a reflex, namely pulmonary pleural and bronchial diseases and one other of cardiac origin not associated with heart failure. This other cardiac cause of dyspnea due to a pulmonary reflex is mitral stenosis, which acts mechanically and not by myocardial failure; the mitral ostium is too small to transmit to the left ventricle all the blood that comes to it from the strong right ventricle, especially when there is a tachycardia from effort or excitement or of paroxysmal nature; the lungs fill up as a result, as was so well stated by Vieussens more than 200 years ago (1715)—see Chapter 26. The second factor, namely anoxemia, comes from failure of either ventricle or both and so may complicate the pulmonary reflex factor; when the right ventricle fails in mitral stenosis, the first factor, namely that due to pulmonary engorgement, is actually decreased and the second factor may change but little one way or the other since it can be caused either by pulmonary stasis or by peripheral systemic stasis.

Secondary causes of dyspnea superimposed upon the primary factors are most commonly effort and excitement, including the very effort of dyspnea itself, which thus starts a vicious circle; cough, nightmares or other sudden fright, paroxysmal tachycardia or atrial fibrillation, pressure from hydrothorax or ascites, and infections and operations.

At first cardiac dyspnea comes only on moderate exertion, but as the degree of failure of the left ventricle increases it comes on slight exertion and finally even when the patient is absolutely quiet. Besides exertion, position is an important factor in the production of dyspnea in advanced cases. There are four reasons for this. When the body is recumbent the blood flow through the heart is greater than in the upright position. It has been reported that the effect of gravity in the upright position relieves the heart of a considerable amount (estimated at about one fourth) of the blood which circulates through it.

when the patient is in the recumbent position, this reduction of work is important in giving the heart some rest. Secondly and similarly, the lungs are also less engorged in the upright position. Thirdly in the upright position there is more room for breathing and free heart action with the diaphragm lower and the pressure from a large liver and ascites less disturbing. And fourthly in the recumbent position the respiratory center is itself directly acted on by the stasis of the venous blood in severe cases which gravity in the upright position at once helps to correct so far as the respiratory center is concerned. The symptom of difficult or impossible breathing in the recumbent position is called *orthopnea*.

An important and interesting symptom of heart failure not always recognized as such may be *insomnia* due to an ill defined orthopnea. In such instances treatment directed to control congestion is likely to be much more effective than the administration of hypnotic drugs which in large doses may result in mental confusion (Wheeler and White 1945).

There is one very important and striking type of dyspnea of cardiac origin due to acute failure of the left ventricle coming on mostly in recumbency at night but also at times on effort in the daytime. This is *acute paroxysmal dyspnea* which may or may not be attended by signs of pulmonary edema or by an unusual respiratory reflex resulting in asthmatic breathing. When asthma complicates this phenomenon of paroxysmal dyspnea due to sudden pulmonary vascular engorgement the condition is called *cardiac asthma*. Paroxysmal dyspnea due to acute failure of the left ventricle is always serious and sometimes fatal (from the associated pulmonary edema or state of shock) but there is another as a rule less grave cardiac cause of such dyspnea with or without cardiac asthma namely *mitral stenosis*. In cases of marked mitral stenosis a sudden moderate or marked tachycardia as from the onset of atrial fibrillation which is so common in mitral stenosis tends to flood the lungs due to overactivity of the right ventricle and the respiratory distress is precipitated. Pulmonary edema due to mitral stenosis can be very serious (see Chapter 26).

Cough and expectoration with sputum which may be blood tinged are frequent with edema of the lungs interstitial and alveolar.

Finally so far as disturbed breathing is concerned there is one other type not so much dependent on myocardial weakness and congestive heart failure *per se* as on faulty circulation in the brain itself as from marked cerebral arteriosclerosis or other cause for depression of the respiratory center. This is *Cheyne Stokes respiration* with its waxing and waning of activity of the respiratory center (see Chapter 3) in well marked cases periods of apnea and hyperpnea of 20 to 30 seconds duration alternate with each other. When Cheyne Stokes respiration occurs in waking hours it is a very serious sign of circulatory failure.

Other symptoms of congestive heart failure are less common than dyspnea and are due in the main to failure of the right ventricle. There is frequently *discomfort from congestion of the liver* more particularly if the liver engorgement is acute along with tenderness in the right hypochondrium. Actually

the very first symptom of right ventricular failure is liver pain on effort due to acute congestion much as dyspnea from pulmonary congestion is the first symptom of left ventricular failure it is not however so impressive (Boyer and White 1942) Also ascites may produce disagreeable pressure sensations and edema of the legs may be painful

Pain is not common in the precordial or substernal regions but there some times is a more or less constant ache in nervous persons with big hearts Weakness is common but not uniform Insomnia headache nervousness mental disturbance and indigestion (the last from congestion of stomach liver and intestines) are frequent In a cardiac patient insomnia should always be investigated as being the possible result of dyspnea digitalis may dispel it more readily than hypnotics Palpitation is rare unless there is a complicating disturbance of rhythm

Fever has sometimes been attributed to congestive heart failure and explained as the result of the inability of the skin because of the edema and disturbance to the peripheral circulation to get rid of excess body heat Such upset of the heat regulatory mechanism of the body may perhaps account on occasion for one degree (F) of fever but fever of any significance that is of two degrees or more has been found to be due always to some complication particularly pulmonary infarction pulmonary infection or rheumatic fever (Kinsey and White 1940)

**Signs** The chief signs of congestive heart failure are those of blood stasis edema and cyanosis (see Chapter 4 for full discussion of these signs) Circulatory stasis may be primarily in the lungs due in the main to left ventricular failure or in liver and dependent parts of the body due characteristically to failure of the right ventricle or it may be evident in all three circulations—pulmonary portal and systemic An important factor which greatly favors the accumulation of fluid in the body in congestive heart failure is the faulty renal function due to inadequate circulation to the kidneys this results in the retention of sodium and water (see Chapter 4)

In the *lungs* the stasis shows itself first by decrease in vital capacity (Chapter 10) due to decrease in the air space often also by emphysema (the lungs being distended) and later still by moist rales beginning at the lung bases and extending throughout the lungs

In the *systemic circulation* the stasis shows itself by engorgement and visible pulsation in the neck (jugular) veins with the patient upright by increase in size of the feet and legs developing into pitting edema and eventually by an extension of edema to thighs hips genitalia abdominal wall thoracic wall and infrequently even to the arms and face Generalized edema is called *anasarca*

In the *portal circulation* stasis is shown by engorgement of the liver and by stasis distal to the liver The liver may increase enormously in size so that it reaches the level of the umbilicus or even lower in a few cases the stomach and intestines are involved also becoming congested and disturbed in function *Ascites* is found in the more severe cases The degree of portal stasis is

often out of proportion to that of stasis in the systemic circulation due probably to the greater degree of obstruction to the blood flow from the hepatic veins than to that in the inferior vena cava combined with a high degree of permeability of the capillaries of the portal system

Even though there is marked portal stasis with engorgement of the liver jaundice is found in congestive heart failure only rarely. When it does occur other factors are responsible in the main acute or chronic liver damage or extensive hemolysis (as from pulmonary infarction the blood pigment from which the congested liver is unable temporarily to handle). Tests as with Bromsulphalein may demonstrate reduction in liver function during acute or chronic congestion.

The accumulation of fluid in the pleural cavities (*hydrothorax*) and rarely in the pericardium (*hydropericardium*) is a further sign of congestive heart failure. It is more common in the course of stasis in the systemic circulation to find hydrothorax in the right than in the left pleural cavity (McPeak and Levine 1946 White August and Michie 1947). The exact explanation of this localization is not clear. It is probably due to greater stasis in the right pleural circulation than in the left either through engorgement or compression of the azygos vein or because the pulmonary circulation in the right lung has a greater height to travel to reach the left atrium than has that in the left lung especially when the patient is inclined, as so often happens to lie on the right side or because of both these factors. Only a part of the left pleural circulation is drained into the vena azygos major by the vena azygos minor the balance emptying into the left innominate vein the flow in which is probably obstructed less than in the azygos veins. When the fluid increases in the right pleural cavity it begins to appear also in the left and finally fluid is found even in the pericardial sac in cases with marked anasarca.

Cardiac enlargement often marked in degree and sometimes acute (due to dilatation) is always evident with congestive heart failure. Frequently murmurs are found due either to organic valve disease or to functional valvular insufficiency. The heart sounds may be unaffected but occasionally they are of poor quality due especially to the weakness of the first sound at the apex so that with tachycardia there may be a so-called tic tac character to the sounds. Now and then with marked ventricular dilatation there is heard the ominous protodiastolic gallop rhythm maximal at the apex in left ventricular weakness and at the lower end of the sternum in right. Arrhythmia is frequent but is just as often absent the chief types are ventricular premature beats and atrial fibrillation.

Accentuation of the pulmonary second sound often reflects the increase in pulmonary blood pressure when the left ventricle fails.

Blood pressure studies with congestive failure show great variations. There may be extreme hypertension lesser grades of hypertension normal pressure readings or hypotension the last being especially significant of cardiac weakness if there has been a rapid or steady fall of pressure to a low level or even a normal level from a previously high level. One sign of the greatest im-

portance usually discovered in the course of sphygmomanometry but often carelessly overlooked is alternation of the pulse frequently found as evidence of left ventricular fatigue even before the onset of frank congestive heart failure (see Figure 33 page 162 and Chapter 8)

Roentgen ray studies are not of great importance in congestive heart failure but they do help to determine the degree of cardiac enlargement especially if there is changing size as in a few cases with acute dilatation (with coronary thrombosis and acute rheumatic carditis for instance) they also help to show by the heart shape the type of lesion present and they afford useful information about congestion of the lungs (engorgement of the lung hilus shadows—see Figure 149—and in extreme cases even pulmonary edema) and about the presence and the degree of hydrothorax Finally fluoroscopy sometimes reveals the weak cardiac pulsations that may accompany failure

Graphic records are of some importance The arteriogram may show pulsus alternans especially after premature beats the phlebogram (jugular pulse tracing) often shows stasis by the combination of the *c* and *v* waves and the electrocardiogram may reveal some serious degree of intraventricular block or *T* wave change findings which are helpful in prognosis The electrocardiogram furthermore quickly gives information about arrhythmias and atrial action and it is frequently a useful guide in the course of treatment changes in the *ST* segment and *T* wave (see Chapter 9) and in the ventricular rate (in atrial fibrillation) affording a control of digitalis therapy The *QT* interval which is a measure of ventricular systole is prolonged in congestive heart failure and shortened by effective therapy consisting of digitalis or other measures such prolongation is probably to be ascribed in large part to the attendant cardiac enlargement chiefly dilatation for digitalis does not shorten systole in normal persons (White and Mudd 1929 Phang and White 1943)

The basal metabolic rate is somewhat elevated with congestive heart failure even to as high as 40 per cent above normal in a few cases the reasons for this elevation if thyrotoxicosis can be ruled out (which is usually done easily) are that dyspnea and cough are often present to increase the work of the body even though the patient is in bed and the myocardium itself as the result of its increased bulk and inefficiency is consuming much more than its normal share of oxygen The blood is not remarkable With considerable renal stasis the urine more or less regularly contains albumin and casts and is decreased in amount (oliguria) and renal function tests may show marked renal insufficiency for example the phenolsulfonphthalein or red test may give readings as low as 10 or 20 per cent in two hours with delayed appearance of the dye in the urine compared to the normal two hour excretion of 60 to 70 per cent and rapid appearance of the dye Also the congested kidneys are unable adequately to excrete salt With restoration of myocardial sufficiency the urine tends to clear and renal function shifts toward normal

The rate of the circulation is slowed in congestive heart failure through the lungs in left ventricular failure and through the systemic veins in right Thus a delay in the arm to-lung time from the normal average of 6 seconds to a



reading of 12 seconds  $\equiv$  determined by the injection of ether (see Chapter 10) indicates congestion in the systemic venous circulation the most common cause of which is right heart failure. If the arm to lung time is relatively normal



FIG 149 Roentgenograms of the thorax during left ventricular failure and following recovery therefrom. Note abnormally large heart and pulmonary edema in *A* with clearing of the pulmonary edema and decrease in heart size after 9 days of treatment in *B*. M.B., female, age 44 with hypertensive heart disease (B.P. 190 systolic and 150 diastolic).

but the arm to-tongue time is delayed from the normal average of 12 seconds to a reading of 24 seconds as determined by the injection of Decholin (or other test substance—see Chapter 10), we have evidence of considerable congestion in the pulmonary circulation commonly ascribable to left ventricular failure or mitral stenosis but not to pulmonary disease per se or to bronchial asthma. Thus in doubtful cases of congestive failure and particularly in distinguishing between pulmonary and cardiac causes of dyspnea these circulatory rate tests are of considerable value.

The output of blood by the heart is decreased and the volume of circulating blood is increased in congestive heart failure both values returning to normal on recovery.

Exercise tests of various sorts have been recommended to determine the presence and degree of congestive failure: the amount of dyspnea and persistent tachycardia and hypertension after stair climbing, walking, running, weight lifting, or respiratory tests have sometimes been considered as criteria of the sufficiency of the circulation. As outlined in Chapter 10 these tests are of but limited value, measuring as they do physical fitness as a whole rather than cardiac strength in particular. The determination by inquiry or observation or both of the patient's reaction to the usual demands of his or her own particular daily life is easier, less harmful, and more accurate and instructive than is judgment of the heart condition by special exercise and respiratory tests.

Finally there is one further method of study of some value, rather in following the condition of a given case with congestive heart failure already present than in determining its presence in the first place. This method is the measurement by spirometer of the vital capacity of the lungs (amount of air that can be expired after the greatest possible inspiration). The amount of the vital capacity normally about 4 to 5 liters in the male and 3 to 4 liters in the female varies inversely with the amount of congestive failure provided other factors such as inexperience in the use of the test and changing pulmonary disease do not enter in. Starting at 0.5 to 1 liter during a period of marked failure the vital capacity may increase rapidly or slowly almost to normal when dyspnea is dispelled by rest, digitalis, and diuretics. To determine the presence of congestive heart failure in the first place, vital capacity studies are less useful than other methods, in particular history taking.

**Course and prognosis.** Although congestive heart failure is always important its course and prognosis vary tremendously with other factors. Thus, contrary to some impressions, it is not enough to know that the heart is unable to maintain a sufficient circulation; it is as I have emphasized before, important and often essential to know what conditions are causing the myocardial insufficiency in order to render a reasonable prognosis and to outline the best plan of treatment. For example, slight congestive failure due to chronic hypertension or mitral stenosis may be easily controlled for many years by moderate restriction of activity and digitalis therapy, while congestive failure, slight at first but rapidly increasing with syphilitic aortitis and aortic regurgitation or with coronary occlusion demands a far graver prognosis, life often lasting but

■ few months to a few years at best with much more restriction of activity and in the case of syphilis with the need of specific therapy if the cardiac condition allows. There are many variables in judging congestive failure—speed of onset, severity, underlying cause, age of the patient, response to treatment and the faithfulness of the patient in maintaining the necessary treatment. Every case must thus be considered individually from all points of view and after careful and complete study. A snap diagnosis of cardiac insufficiency by a history of dyspnea and by observation of cyanosis and engorged veins in the neck is inadequate. It is based on but a small though important part of the situation, the end result of serious heart disease and heart strain. A detailed prognostic analysis of congestive heart failure has revealed that marked cardiac enlargement, old age and the presence of the more serious uncontrollable precipitating factors and complications are the most unfavorable findings (Boyer, Leach and White, 1941).

To estimate an average duration of life after the onset of congestive failure ■ ■ ■ misleading because of the great variations that exist, but the severity of the condition in general ■ ■ ■ shown by the fact that such an average ■ ■ ■ but a few years. Many old persons have dyspnea, the first evidence of congestive failure for many years without desire or need of seeking medical advice, and the fact that such cases frequently are not included in statistical studies makes any estimate of duration of life after the onset of congestive failure very difficult.

There is, however, one condition in the course of congestive heart failure that carries with it a serious and sometimes rapidly fatal prognosis. That ■ ■ ■ paroxysmal dyspnea with or without cardiac asthma. Life often lasts but a few months and at best but a few years after the first attack, except rarely, but life can undoubtedly be much prolonged by adequate therapy, especially digitalization and limitation of physical strain.

Death in congestive heart failure rarely comes from the failure alone but is almost invariably due to some last straw, most commonly pulmonary infarction or infection, which may be difficult to diagnose ante mortem.

**Complications.** The complications of congestive failure are varied, the congestive failure itself ■ ■ ■ frequent complication of many conditions already noted. Circulatory stasis disturbs the function of many organs: lungs, liver, stomach, intestines, kidneys and brain. Undoubtedly the coronary circulation is also often interfered with, to aggravate still further the myocardial weakness. Engorgement of the pulmonary circulation and edema of the lungs not only are a menace to life through asphyxiation but so affect the lungs themselves that they are easy prey to extensive hemorrhagic infarcts on the occasion of pulmonary embolism, which is one of the most common and important complications of heart failure, arising as it does from phlebothrombosis due to stasis in the legs (see Chapter 28). Chronic stasis in the liver can lead to atrophy and compensatory hyperplasia, with the end stage of cirrhosis in some very chronic cases of mitral stenosis (and constrictive pericarditis). Gastric stasis predisposes to ulcers of the stomach and intestinal stasis to chronic indigestion and emaciation and to hemorrhoidal venous engorgement. Renal

stasis can cause albuminuria renal insufficiency nitrogen retention and even rarely uremia Splenic stasis is apparently less important Congestion of ovaries and testes may cause decrease in function sterility miscarriages and disturbances of menstruation (amenorrhea menorrhagia and metrorrhagia) Massive edema of the extremities may result in ulceration of the skin and infection Cerebral edema and insufficient circulation can cause a sluggish mental state and even delirium and coma in old persons who have narrowed arteries if they have already a tendency to an unstable mentality Finally terminal infections particularly pneumonia are common in the weakened condition of patients with congestive heart failure

**Treatment** The treatment of congestive heart failure may be conveniently divided into seven parts as follows (A) rest (B) use of digitalis and allied drugs (C) diuretic drug therapy (D) use of other drugs including cathartics and hypnotics (E) the regulation of diet (salt and fluid intake) (F) other therapeutic measures including venesection and (G) environment and other factors Attention has already been called to the fact that in a case of congestive heart failure it is not enough simply to treat the failure it is essential from the standpoint of intelligent treatment to discover when possible what is back of the failure as for example thyrotoxicosis

**A Rest and exercise** The two most important remedies that we possess for the relief of congestive heart failure are rest and digitalis (or strophanthin) therapy All other measures though occasionally lifesaving and often useful are in general far less valuable The amount of rest to be prescribed depends on the individual case For patients who have dyspnea on moderate exertion only there need be merely slight restriction to avoid the exertion which produces symptoms sometimes however a period of a few weeks of complete rest is wise in such cases to build up reserve strength and to prolong life It is necessary to differentiate carefully in such mild cases between the dyspnea of heart failure and that of poor general physical condition or neurocirculatory asthenia when more exercise rather than less may be advisable Also it is important usually to allow a patient with heart disease but without failure to take as much exercise as he reasonably and safely can with periods of rest as needed because it is physical exercise that helps to maintain a state of general good health undoubtedly the proper functioning of the peripheral circulation and of the diaphragm resulting from reasonable exercise aids the heart in its work The most practicable exercise is walking and this is also uniformly satisfactory it can be graded easily by three factors—distance speed and slope (hill climbing) Other mild exercises like easy golf and croquet may be encouraged at times

When there is a definite amount of congestive failure at rest or on very slight exertion exercise including sexual intercourse must be prohibited and absolute rest at least for a few days should be prescribed This rest should not be maintained recumbent for as already stated the recumbent position is not a restful one so far as the heart is concerned An upright or semiupright position in comfortable chair or adjustable bed is the best arrangement for

obtaining the full benefit of absolute rest a special cardiac bed such as that shown in Figure 150 is particularly helpful for it is larger and better adapted to prolonged rest treatment than a chair and also permits ample opportunity



FIG 150 Photograph demonstrating the treatment of congestive failure by the "Lawson Tait" cardiac chair bed (Lewis) and by Southey tubes. The bed is shown with the head partly raised and the foot partly lowered about midway between the possible extreme positions of flat bed and chair. The Southey tubes are inserted in both legs or feet (usually two tubes in each) so that they drain edema fluid by gravity into bottles at the foot of the bed (the bottles may be placed in containers fastened to the foot of the bed). Penicillin is given to prevent infection during their use. The tubes have small holes or slits through which the fluid passes by capillary action from the subcutaneous tissue into the fine rubber tubing. A trochar, the handle of which holds the tubes when not in use, is employed to insert the tubes vertically into the skin and subcutaneous tissue up to their cuffs over which the rubber tubing fits. The trochar and tubes are reduced to 2/5 natural size.

for changing the patient's position easily. There is a great difference between ordinary rest in bed and absolute rest and this difference may mean the difference between failure and success in the treatment of serious congestive failure. With ordinary rest in bed the patient moves about a good deal by himself, reaches for various things, feeds himself, holds a book to read, sometimes writes or dictates, and often entertains visitors. With absolute rest he does as little as possible himself and is very carefully nursed; he is lifted to different positions, is fed, is not allowed to reach for objects or to hold them to read or to write, he is denied all but a very few visitors of calming and pleasing influence, the stimulating effect of noises is reduced to a minimum, to while away some of the waking hours, entertaining light and restful literature may be read to him for short intervals, all business and family cares are banned. It is not always easy to start such a regime but with full explanation of its nature and purpose and sometimes with the help at first of sedatives such as bromides or of hypnotics if needed, the absolute rest therapy may prove a great success. Generally a few days of such treatment suffice, along with drug therapy, when improvement is marked, more activity may be allowed. A mild climate is helpful during convalescence.

**B Digitalis**, or foxglove (either the purple (purpurea) or the yellow (lutea and lanata)) is one of the most valuable of drugs; its intelligent use is a real triumph in the practice of medicine, permitting the accomplishment of results not possible by unaided nature. Up to 175 years ago digitalis introduced as a medicinal herb and given its name by Fuchs in 1542, had been applied externally as a counterirritant or used internally as an emetic and purge by the medical profession when used at all. In 1785 Withering formally introduced it in the treatment of edema, having discovered in 1775 that it was one of the ingredients of an herb mixture used successfully in the treatment of obstinate dropsy by an old woman in Shropshire, England. He enunciated clear rules for its use which, however, were followed but little during the next century and it has been only during the last generation that its true worth has been appreciated.

Withering, William (1741-1799) Shropshire, England. *An Account of the Foxglove and some of its Medicinal Uses With Practical Remarks on Dropsy and Other Diseases*. M. Swinney, Birmingham, 1785.

Pertinent quotations from this important volume including therapeutic directions are as follows:

After having been frequently urged to write upon this subject and as often declined to do so from apprehension of my own ability, I am at length compelled to take up the pen, however unqualified I may still feel myself for the task.

The use of the Foxglove is getting abroad, and it is better the world should derive some instruction, however imperfect from my experience, than that the lives of men should be hazarded by its unguarded exhibition.

Fuchsius in his hist. stirp. 1542 is the first author who notices it. From him it receives its name of *Digitalis* in allusion to the German name of Fingerhut.

which signifies a fingerstall from the blossoms resembling the finger of a glove

In the year 1775 my opinion was asked concerning a family receipt for the cure of the dropsy I was told that it had long been kept a secret by an old woman in Shropshire who had sometimes made cures after the more regular practitioners had failed I was informed also that the effects produced were violent vomiting and purging for the diuretic effects seemed to have been overlooked This medicine was composed of twenty or more different herbs but it was not very difficult for one conversant in these subjects to perceive that the active herb could be no other than the Foxglove

Withering reported 163 cases treated with digitalis some of which were successful and some not The dropsies were usually treated successfully while uncomplicated cases of tuberculosis remained unchanged

Withering noted communications from correspondents citing cases A letter from Mr Wainwright a surgeon in Dudley had the following recommendation Collect it in a hot dry day when the petals fall and the seed vessels begin to swell The leaves kept to the second year are weaker and their diuretic qualities much diminished It will therefore be necessary to gather the plant fresh every season

Withering himself proceeded, the more we multiply the forms of any medicine the longer we shall be in ascertaining the real dose Foxglove when given in very large and quickly repeated doses occasions sickness vomiting purging giddiness confused vision objects appearing green or yellow increased secretion of urine with frequent motions to part with it and sometimes inability to retain it slow pulse even as slow as 35 in a minute cold sweats convulsions syncope death

Directions for use I give to adults from one to three grains of this powder [powdered leaves] twice a day In the reduced state in which physicians find dropsical patients four grains a day are sufficient

If liquid medicine be preferred I order a dram of these dried leaves to be infused for four hours in half a pint of boiling water adding to the strained liquor an ounce of any spirituous water One ounce of this infusion given twice a day is a medium dose for an adult patient or once in 8 hours or  $\frac{1}{2}$  ounce at a time About 30 grains of the powder or eight ounces of the infusion may be taken before nausea commences

*Let the medicine therefore be given in the doses and at the intervals mentioned above let it be continued until it either acts on the kidneys the stomach the pulse or the bowels let it be stopped upon the first appearance of any one of these effects*

#### Inferences

I That the Digitalis will not universally act as a diuretic

"IV That if this fails there is but little chance of any other medicine succeeding

"IX That it has power over the motion of the heart to a degree yet unobserved in any other medicine and that this power may be converted to salutary ends"

1 *Action of digitalis* The action of digitalis on the heart is threefold (a) In the first place it depresses the pacemaking function of the sinoatrial node and also of the atrioventricular node with the resulting tendency for the heart rate

to be slowed when there is normal rhythm or in rare cases when there is atrio-ventricular nodal or idioventricular rhythm. This is in part at least a vagal effect and may be removed by paralyzing the vagus nerves by atropine sulfate 1 to 2 mg ( $\frac{1}{100}$  to  $\frac{3}{100}$  gr) subcutaneously. In different individuals there is often a variation of the degree of influence of digitalis on the rate in normal rhythm. When this depressing effect is not very apparent it can sometimes be easily brought out by pressure over the right carotid artery. Sinus arrhythmia as well as sinoatrial bradycardia are common results of digitalis action. These effects of the drug on the pacemakers of the heart enter little or not at all into therapy but they should be known for they explain some of the by-effects of the drug action. There are some cases of the Morgagni-Adams-Stokes syndrome due to paroxysmal heart block which is set off when the normal sinus rhythm rises to a rate say of 80 at which the a-v junctional tissues are unable to conduct the impulses. It may be possible in such cases by the careful use of digitalis to keep the sinus rate below this critical level without further depression of a-v conduction. In rare cases with large doses of digitalis it is even possible to paralyze the atria altogether or to irritate the atrioventricular node so that it escapes from atrial control and gives rise to a regular independent ventricular action at normal or somewhat elevated rate.

(b) A second effect of digitalis on the heart is on conduction. This occurs all through the heart muscle with increase in the refractory period of atrial and ventricular muscle so that atrial flutter for example is converted into atrial fibrillation (Chapter 33), intra-atrial block and intraventricular block (of either bundle branch generally of slight degree) as evidenced by changes of the P and QRS waves of the electrocardiogram (Chapter 34) have in rare cases been ascribed to the digitalis effect. The most marked and important influence on conduction however is on the main tract between atria and ventricles namely the atrioventricular node (of Tawara) and bundle (of His). Various grades of atrioventricular block are easily induced by digitalis from slight delay in conduction up to complete block in susceptible individuals. Again the effect is in part vagal but apparently only in part for vagal paralysis often fails to obliterate the effect of large doses of digitalis. Vagal stimulation (by carotid sinus pressure) usually increases easily the grade of block already produced by digitalis or brings it out when latent. The effect of smaller doses of digitalis is apparently largely vagal the heart rate escaping to high levels as the result of sympathetic stimulation from exercise or excitement while large doses have a direct nonvagal effect which may be necessary to keep the heart rate really under control.

It is this depressant influence of digitalis on conduction that explains half the virtue of the drug. It has long been known that there is one type of patient with congestive heart failure especially helped by digitalis therapy sometimes with astounding success. This type is the patient who has also atrial fibrillation with more or less rapid ventricular rate. As noted in Chapter 33 atrial fibrillation is at the very first accompanied by a certain degree of atrioventricular block the ventricles being unable to respond to the atrial rate of 400 more or



less per minute. This irregular grade of atrioventricular block is quickly increased by digitalis in full dosage and the heart rate falls to normal or even to low figures with a great increase in the intervals of rest for the ventricles (long diastolic pauses) and usually with coincident striking relief of the symptoms and signs of congestive failure. The reduction of rate of as much as 100 beats per minute which sometimes occurs in such cases for example from 160 to 60 means sparing the heart muscle an unnecessary and often ineffective amount of labor consisting of 6 000 beats an hour or well over 100 000 beats a day. Even a reduction of but 50 beats which is very common say from a rate of 120 to one of 70 means an omission of 72 000 contractions a day. This is obviously a tremendous relief for an overworked heart. There is no wonder that apparently miraculous recovery sometimes results. With atrial flutter digitalis is often very useful in reducing a fatiguing heart rate for example from 150, with atrial rate of 300 to 75 due to the increase of heart block from 2 to 1' to 4 to 1, the atrial rate remaining at 300 in atrial flutter however digitalis tends to have another effect already mentioned namely to convert the flutter into fibrillation by the production of intra atrial block with the ventricular rate still well controlled by the drug action on atrioventricular conduction. With normal rhythm this influence of digitalis on conduction is usually but slight and often not evident at all.

(c) A third effect of digitalis on the heart is on contraction. In some manner not yet understood the tone of the heart muscle and the completeness of contraction when there are dilatation and failure are much increased by digitalis. These effects in man are far more apparent in cases of normal rhythm with congestive failure than in patients with atrial fibrillation where they may be masked by the effect of the fall in heart rate. It has been sometimes erroneously thought and taught that digitalis therapy is effective only in the presence of atrial fibrillation in the manner described in the paragraph above. Digitalis is often though as a rule less dramatically effective when there is congestive failure with normal rhythm. To withhold digitalis from such cases on the mistaken notion that it will be ineffective constitutes an important therapeutic error. To be sure digitalis therapy in the presence of normal cardiac rhythm is not always effective and its success averages below that when atrial fibrillation is present nevertheless it is often strikingly beneficial and sometimes it is life saving. The effect of the drug on contraction undoubtedly plays some part also in the improvement of cases of atrial fibrillation under digitalis therapy along with the reduction of heart rate. Even in the presence of atrioventricular block of high grade the increase of contractile power may control congestive failure without any danger though the degree of block should be followed closely and the drug used with great caution if there is any threat of the Morgagni Adams Stokes syndrome. The myocardial effect of digitalis is further shown by depression of the *ST* segments and *T* waves of the electrocardiogram.

The effects of digitalis on the rest of the body are varied. As a rule they are absent or slight until large doses have been administered. Some of the effects

are reflex due to the action on the heart but some are direct effects on nervous and other systems

One of the apparent effects that has been noted by several investigators is that on the veins both systemic and portal with constriction acting to aid in the return of blood to the heart

Serious *toxic effects of digitalis* on the heart may occur if overdosage is allowed but such extreme effects are rare Atrial paralysis atrial fibrillation various high grades of heart block a coupled rhythm due to ventricular premature beats every second beat idioventricular rhythm ventricular paroxysmal tachycardia and ventricular fibrillation have all been induced in man or in animals by massive doses of digitalis When any of these disorders of cardiac mechanism are found to result from the digitalis given and not primarily from other factors the drug should be discontinued for a high percentage (50 to 90 per cent) of the lethal dose has probably been given by the time such disorders are found It is also of interest and importance to know that vigorous diuresis in a digitalized patient may release enough additional digitalis into the blood stream from the tissues of the body to produce temporary toxic effects

The earliest and commonest systemic toxic symptoms are malaise headache anorexia and nausea Later on, vomiting visual disturbances diarrhea and even cerebral disturbances may occur If any of these symptoms are pronounced the drug should be omitted for a while and then resumed with care It is important always when searching for toxic symptoms to inquire whether there is blurring of vision or disturbance of color vision—in the latter case objects appear usually yellow or green (Purkinje 1839) Such visual disturbance may be present but not complained of at once being masked perhaps by other toxic symptoms Finally there are individual variations in the ease with which digitalis produces toxic as well as beneficial effects every case must be considered individually

Allergy to foxglove is excessively rare It has been reported (Cohen and Brodsky 1940) but I have not encountered an instance myself among a good many thousand cases The patients whom I have seen who have been easily nauseated or otherwise upset by the drug are those who dislike the taste even when coated tablets are used (regurgitation still gives them the taste) or dislike the idea of taking the drug at all or those who have previously been made sick by it which is evidence of the wisdom of avoiding overdosage to start with and of the art of persuasion when the drug is badly needed

2 *Therapeutic indications for the use of digitalis* There are five chief indications of the need of digitalis therapy (a) congestive heart failure with or without atrial fibrillation atrial flutter or heart block (b) atrial fibrillation or atrial flutter with rapid ventricular rate when quinidine sulfate alone is not administered at once (see Chapter 33) (c) obstinate paroxysmal tachycardia or premature beats which may infrequently be abolished by digitalis (d) as a therapeutic test when it is uncertain whether or not there is a slight degree of congestive failure as in the case of old persons with slight dyspnea on exertion of victims of chronic pulmonary emphysema with a higher degree of

dyspnea than is readily attributable to the lung condition alone and of patients with massive pulmonary embolism and (c) as a means of delaying or warding off heart failure altogether and even perhaps of preventing further cardiac enlargement in patients with serious chronic heart strain from any cause who already have big hearts. For other conditions digitalis should not be used much of it has been wasted in the past and many patients with all manner of illnesses have been made at least temporarily miserable by the toxic effects of digitalis with no resulting benefit. The drug should not be used in any way routinely in preparation for surgical operations (unless there is serious heart strain congestive failure or atrial fibrillation) in the treatment of surgical or postoperative emergencies and collapse during anesthesia in the therapy of infectious diseases or in treating constrictive pericarditis (acute or chronic) in the absence of atrial fibrillation or flutter or neurocirculatory asthenia. The indiscriminate use of digitalis is to be strongly deprecated.

There are no contraindications to the use of digitalis when the drug is really needed except the very rare Morgagni Adams Stokes syndrome in high grade heart block (even in such cases there are exceptions—see page 943) and the very rare individual hypersensitivity to the drug action. Complete heart block without syncopal or faint attacks is not a contraindication.

**3 Preparations of digitalis** The ways in which digitalis is prescribed have varied very much with the years. After its introduction by William Withering and for a hundred years or more it was used mostly in the form of the dried leaf and in tinctures and infusions. At the beginning of the present century the tincture and powdered dried leaf were used chiefly. Gradually the tincture itself has been largely given up in this country so that pills or capsules of standardized dried leaf have been in current use more or less routinely during the last two decades and have proved a very satisfactory way of giving digitalis. However during recent years purified active principles and extracts of digitalis derived from the purple and yellow foxglove have come more and more into use and have the advantage of less need of animal standardization and of simple use by weight alone. An interesting preparation for investigative purposes has been introduced by growing radioactive digitalis in an atmosphere of radioactive carbon dioxide (Geiling et al 1949).

In the previous editions of this book there has been considerable reference to cat units and to the use of frogs for the standardization of digitalis. Fortunately in the future although such testing is still necessary when one uses the whole leaf it will become less and less necessary to refer to such standardization in discussing treatment with digitalis. In the evolution of the improvement of digitalis preparations a generation ago the strict insistence on some method of standardization helped greatly in getting rid of inert preparations on the market (Pratt and Morrison 1919). Human standardization has been recommended (Gold et al 1942) and as a matter of fact is actually the best method of all in dealing with preparations in need of testing despite its practical difficulty and the considerable variations of sensitivity in individual subjects.

These extracts of digitalis more currently in use today include one of the very old purified glycosides first introduced over a hundred years ago by Nativelle (1845). This is digitoxin also called Digitaline Nativelle Purodigin and by other trade names. It is an effective preparation almost a thousand times stronger in its effect by mouth than standardized dried digitalis leaf so that 0.10 mg of digitoxin is approximately equivalent to 0.10 gm of dried leaf. It is my experience however that it is not so strong and that for the human 0.15 mg of digitoxin is equivalent to 0.10 gm of digitalis leaf. Other active principles include digitonin, digitalein, digoxin, Digalen and lanatoside C (Digilanid from digitalis lanata).

One of the chief advantages of these purified preparations is that they can be more readily given intravenously in full strength. Digitoxin for example given intravenously has much the same effect as when given by mouth. The method of administration and exact dosage will be referred to below.

**4. Method of digitalis administration and dosage.** There has been considerable confusion in the past as to the strength of digitalis leaf in the *US Pharmacopeia*. To follow the international standard it was necessary to increase the strength per weight of the drug at the time of USP XI (1936) and USP XII (1942) from that of the previous standard of USP X (1926). The result of all this change was that the standard strength of digitalis leaf now as compared with the strength twenty years ago is in the ratio of 85 to 100; thus a grain of digitalis leaf now is equivalent to 0.85 gr of twenty years ago and a dose of 1.5 gr is equivalent to 1.28 gr of the earlier strength. Because of the greater ease of slow digitalization years ago than now one preparation, namely Digitora (Upjohn), has held to the old dosage and consists of 1.28 and 0.85 gr tablets for convenience in routine use as will be discussed below under dosage. At first when this change in strength took place there was a good deal of digitalis intoxication because of the failure of the medical profession in general to be aware of the greater strength of the preparations; this situation has now been largely corrected.

The methods of digitalis administration are several. The most common and generally useful is by mouth, applicable to at least 95 per cent of all cases needing the drug. Parenteral injections into vein or muscle and rectal suppositories should be reserved for the very few cases in which the drug is urgently needed and cannot for some reason be given by mouth.

There are three important aspects in the matter of giving digitalis: (1) digitalization, that is, saturation with the drug; (2) maintenance of its effect; (3) testing its value in a given case. Also there are various methods, namely: (1) the common oral administration; (2) the infrequently needed intravenous use; and (3) rectal administration.

Digitalization consists in the administration of enough of any digitalis preparation to obtain the maximal therapeutic effect with as little toxic action as possible. Such digitalization may be rapid or slow and by mouth or by vein. Very few patients, especially in these days of more enlightened treatment, require emergency rapid digitalization. When this is necessary the intravenous

route is generally the most suitable. However the result may be quite satisfactory by oral medication provided a rapidly acting drug is used. Figure 151 illustrates the speed with which digitalization can be secured within a few hours by intravenous medication with certain preparations for example lanatoside C or Cedilanid and ouabain or strophanthin. A dose of 0.8 mg of Cedilanid (1 cc = 0.2 mg) repeated in full or half dosage in four hours if necessary is an effective method of rapid digitalization. 0.5 mg ( $\frac{1}{2}$  cc solution) of strophanthin or ouabain is also effective and somewhat more rapid in its action. In each case the effect begins in a relatively few minutes reaching its maximum within a few hours, the exact time varies somewhat from patient to patient. Digitoxin may also be given intravenously, in the initial dose of 0.6 mg to 1.2 mg or more for full effect quite rapidly, the special advantage of digitoxin is that it can be given in the same dosage also by mouth with somewhat slower but usually satisfactory result in the course of a relatively few hours. Digitoxin when given by mouth is absorbed essentially in toto and therefore can be used in uniform doses.

Standardized digitalis leaf in powdered form may also be used for digitalization by mouth. Its strength is about a thousandth of that of the pure digitoxin and therefore, in the course of twenty four hours about 1.2 gm need to be given. Since each pill of digitalis is conveniently put up in 0.10 gm ( $\frac{1}{10}$  gr) the total amount may be given in the form of 0.3 gm that is three pills four times in twenty four hours or even 0.4 gm at a dose at four hour intervals, thus getting in the full amount in the course of eight hours which is rapid enough for the great majority of patients needing quick digitalization. The advantage of divided dosage of any of these preparations is that some individuals are very sensitive to the drug no matter in what form it is given if there are toxic effects after the first second or third dose the later doses may be reduced or omitted. It is important to try to avoid serious toxic effects from digitalis because of the common need for the constant use of digitalis for weeks months or years after it has once been given. Happily digitalis is as effective after ten years as it is the first day. There is not the acquirement of tolerance to the drug hence no need of increasing the dosage with the passage of time as in the case of so many other drugs. Most of the so called allergy or sensitivity of patients to digitalis is the physical or psychologic repugnance to the drug following a toxic effect. I myself experimentally took large doses of digitalis over twenty years ago and I still have a strong memory of the disagreeable taste at the time of toxic symptoms from it. Therefore the one dose method of digitalization is generally to be avoided unless the situation is very critical otherwise and we are dealing with a large patient who is apparently not hypersensitive to medicines in general.

Preparations of the whole leaf, for example Digifolin are also available for intravenous use and may be given thus in about the same dosage and time intervals as the pills by mouth.

For slower digitalization it is very convenient to use one week's time for saturation with the drug for example one may prescribe the medicine to an



ambulatory patient in hospital clinic or private office and have the patient return in one week to determine the effect. For this purpose the digitalizing dose may be spread through the seven days adding a little extra for excretion each day. Thus if one uses dried whole digitalis leaf of the current strength one may give a 0.1 gm (1½ gr) pill twice a day for a week or three times a day for four days followed by one pill daily thereafter. A few patients need slightly larger doses than this and a few patients slightly smaller but this is the average for the majority of adult patients. If one uses digitoxin one may give three 0.1 mg tablets daily for a week or somewhat more the first half of the week with maintenance dosage afterward of 0.1 to 0.2 mg. Digitoxin is available in 0.10, 0.15 and 0.20 mg tablets. I have found the tablet of 0.15 mg the most suitable of all as a daily ration in the great majority of cases.

There are many other preparations of digitalis which now are all quite satisfactory for digitalization. One of the most useful of all the preparations of the dried leaf is that of Digitora which has kept the old standard strength a very convenient strength for slow digitalization which after all is the best method for the great majority of patients needing digitalization. One tablet of Digitora equals 1.28 gr and can be given three times a day for one week to get just about the right saturation for the average patient whereas 0.1 gm (1.5 gr) of the current strength of digitalis three times a day for a week is too much for most patients and may induce toxic and therefore undesirable symptoms at the end of the week. For rapid or slow digitalization it is possible to give digitalis rectally in the form of suppositories, but these in general are not so reliable since they are not always absorbed adequately and they are sometimes irritating. Hence this is the least desirable way of administering digitalis, although suitable in rare cases.

A point of much concern in the past has been the question of the dosage with respect to the size of the patient and formerly much calculation was carried out from the standpoint especially of the amount of the drug needed for rapid digitalization. At one time 0.1 gr of the leaf was considered necessary for every ten pounds of weight and although this in general may still hold there have been so many exceptions to the relationship of the patient's weight and dosage that we no longer bother about such accurate calculation which really is misleading. For a very large person we may rightly prescribe larger doses and for a very small person a decreased dosage but the wide range of the average between these two extremes does not need to alter what has been written above and what follows below. For children the dosage of course must be less for a child aged 10 to 12 years half the adult dose is to be advised and for the infant about one quarter.

*Maintenance of digitalis effect.* One of the greatest advances in the treatment of heart disease that has occurred in the last generation has been the realization of the importance of the maintenance of digitalis effect. Years ago it was customary to give courses of digitalis with strikingly beneficial effect each time but with the result that between courses of digitalis there would tend to be a recurrence of myocardial insufficiency and often of severe congestive failure. As time passed a few individuals became aware of the vital need of maintain-

ing the full digitalis effect in almost all patients who once needed it. Thus we have done away in large part with two common occurrences of the past. The first was the arrival in the emergency wards of the hospitals of cardiac patients with a sudden onset of pulmonary edema or acute distress otherwise due to rapidly developing heart failure or the emergency summoning of physicians to homes or places of work to treat these people. These accidents still occur but in my experience they are very much less frequent than they were twenty five to thirty years ago. Second, one does not see what one used to the rapidly recurrent anasarca in patients who after digitalization have been allowed to escape from its effect.

For the maintenance of digitalis action there are numerous oral preparations available, the most common and practical being the whole dried leaf itself in tablet or pill form in the dosage of 0.1 to 0.06 gm ( $1\frac{1}{2}$  gr to 1 gr) daily. Such a tablet or pill may be given daily for weeks, months or years to maintain the excellent effect as shown by the persistence of a satisfactory heart rate in the presence of atrial fibrillation or by the failure of a return of evidences of myocardial failure with congestion. Some patients need the larger dose and are not made sick by it; others can get along with the smaller dose better, and a good many do best with a dosage in between, for example 0.1 gm ( $1\frac{1}{2}$  gr) one day and 0.06 gm (1 gr) the next day and so alternately thereafter. Sometimes it is convenient to put up a capsule of  $1\frac{1}{4}$  gr (0.82 gm). Also conveniently digitoxin can be used for maintenance in the dosage by tablet of either 0.2 or 0.1 or best of all of 0.15 mg daily. Cedilanid may be given in daily rations of an average of 0.25 mg and digoxin in a daily dose of 0.5 mg. Liquid preparations can still be used although they are much less commonly employed in this country today. The tincture is a reliable preparation of digitalis consisting of a 10 per cent solution. This can be given in a dose of 1 cc (15 minims) corresponding to 0.1 gm of the dried leaf; the dosage of tincture by mouth can thus be calculated readily.

Electrocardiographic control of digitalis therapy is often very helpful. On occasion the electrocardiogram will show definite effects of digitalis action just before beneficial effects become evident and also on occasion toxic effects may appear first in the electrocardiogram in the form of bigeminy and marked depression of the *ST* segments or prolongation of the *PR* interval before they become manifest as noted above in the form of nausea, vomiting, intestinal irritation and disturbance of vision. Figure 152, page 832 shows full digitalis effect in the electrocardiogram of a case of mitral stenosis with atrial fibrillation.

Of considerable interest and importance has been the gradual development of tests of the concentration of digitalis in the blood, one of the most recent of which a polarographic determination has been reported by Hilton (1949). It is to be hoped that a routine practical determination may become possible.

Until recently the cost of purified preparations has been so much greater than that of the leaf in powder or tincture form that on the basis of expense many have preferred to continue with the whole leaf. However, as time goes on and costs come down, the purified preparations will be more and more



employed because of the simplicity of the dosage without need of animal standardization

Finally on occasion it is useful to test the effect of digitalis in any given case where myocardial failure is suspected or where there is some important com

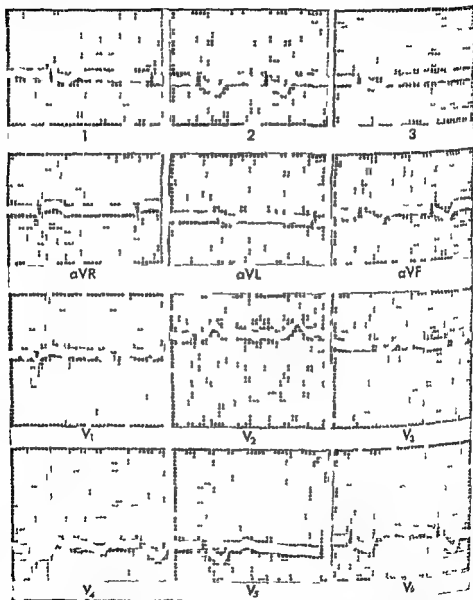


FIG 157 Electrocardiogram in atrial fibrillation with full digitalis effect male age 52 (A) Bipolar limb leads 1 2 and 3 (B) unipolar limb leads aVR aVL and aVF (C) six precordial leads V<sub>1</sub> to V<sub>6</sub> inclusive Note especially the slow heart rate and the depressed (digitalis) ST segments and flattened T waves in Leads 1 2 3 aVL aVF and V<sub>1</sub> to V<sub>6</sub> inclusive Time = 0.04 and 0.20 second amplitude 1 mm = 0.10 mv

plication that may prevent its full action. The same methods of administration as noted above that is of rapid or slow digitalization and maintenance of effect are to be employed but now and then one may want to use at the start small or moderate dosage without full saturation first. Where the need is not so great full digitalization is not so urgent and some benefit may well come from smaller doses such as the so-called tonic dose of 0.1 gm (1½ gr) or 0.06 gm (1 gr) of the dried leaf daily. It is difficult and sometimes impossible to prove or disprove the advantage of this but there is reason to believe that such tonic dosage in the absence of heart failure may help to prevent or delay increasing enlargement of the heart and future failure in cases of constant heart strain as from important valvular disease or hypertension.

There are only two drugs besides digitalis which have digitalis like action that are of much worth. They are *strophanthin* or *ouabain* and the newly standardized active *glucosides of squill* (called variously as Scillonin and Urganin).

5 *Strophanthin (ouabain)* has been proved effective in emergency treatment but its superiority over an ample intravenous dose of digitalis or its glucosides (digitoxin and lanatoside C for example) is debatable. However experienced workers with strophanthin clinically chiefly those trained in the continental European and Latin American clinics report that the drug is superior to digitalis in certain cases for two reasons: (1) because of its more rapid full action in emergencies (shown by Eichna and Taube 1943) particularly when the heart rhythm is normal in acute cardiac failure and (2) because it is thought to have a greater stimulating effect on a failing myocardium in the degenerative types of heart disease (hypertensive and coronary). Strophanthin or ouabain injected intravenously in the dose of ¼ to ½ mg (1/240 to 1/120 gr) never more may result rapidly in great improvement with the saving of life or the clearing of the heart failure. The dose may be repeated in 12 hours and then once every day or two as a ration (1½ to ½ mg) if necessary but it is better to begin full doses of digitalis by mouth within 12 hours of the emergency injection of ouabain so that the digitalis will become effective at a time when the transient effect of the ouabain is wearing off. 0.2 gm (3 gr) of the standard powdered leaf three times daily for two days should suffice before dropping to a ration of 1 or 1½ gr daily. It is largely a matter of choice and custom whether one uses digitalis or strophanthin in emergency treatment. On the European continent and in South America strophanthin is often employed successfully while here in the United States digitalis has been preferred. If it seems desirable to use strophanthin and digitalis has been previously given an interval of forty-eight hours should be allowed to elapse before the strophanthin is administered intravenously so that danger of poisoning may be prevented.

Strophanthin when given intravenously begins to act appreciably on the heart in a very few minutes (five to twenty) with full effect probably in an hour's time and maintenance of the action for twelve to twenty-four hours. Digitalis given intravenously in potent dosage takes about the same length of

time as strophanthin for initial effect, or perhaps a little longer a definitely longer time for full effect (two hours) and its action lasts somewhat longer (one or two days) (Wyckoff and Goldring 1927 Pardee, 1928) Digitalis by mouth is slower to act and yet rapid enough in its effect in most cases showing definite action in two or three hours with full effect in about twelve hours and persistence of action for several days When full digitalization by mouth has been effected an interval of ten days to two weeks is necessary before all the drug disappears from the system

6 *Squill* The active principle of squill may be used by mouth advantageously in the very few cases who need digitalis but cannot take it because of a hypersensitive reaction or very strong prejudice against the taste It is prescribed as scillaren (Scillonin) or as Urganin in tablet form in the dosage of 0.8 mg (1/80 gr) of the former or 1.0 mg (1/60 gr) of the latter as equivalent to 0.1 gm (1 1/2 gr) of standardized digitalis

7 *Other digitalis like drugs* Other drugs of the digitalis group including strophanthus when used by mouth are inferior to digitalis and squill in effectiveness and reliability they include apocynum and convallaria A newer drug (a cardiac glycoside) with a rather rapid stimulating myocardial effect has been introduced under the name *thevetin* it comes from the kernels of the bestill nuts of a tropical tree *Thevetia neruifolia* and is related to apocynum given intravenously it has had in some cases of congestive failure an effect even greater in rapidity than strophanthin (or ouabain) further study of its clinical applicability has been in progress (Arnold Middleton and Chen 1935 Chen personal communication 1942, 1949 Modell et al 1948)

Very rarely digitalis cannot be taken even in small dosage because of its poisonous effect in a particularly hypersensitive individual It is fair and advisable in such a case to try one after another of the drugs of the so-called digitalis series until one is found that is to some degree effective without being toxic It may be assumed as a general rule however that the toxic and therapeutic effects of various preparations of digitalis or of other drugs of the digitalis series are parallel a preparation that can be taken in large dosage without toxic effects is likely to be therapeutically inactive and a preparation that is very active therapeutically tends quickly to cause toxic symptoms One of the drugs of the digitalis group namely squill has a reputation as a diuretic but this reputation is probably based as is that of digitalis on inaccurate observation Its diuretic effect is secondary to improvement in the circulation there is no primary diuretic action Finally it is very important to remember that rest alone will frequently give rise to diuresis when there is edema

8 *Chart of digitalis effects* To follow accurately the effect of digitalis squill or strophanthin in congestive failure it is well to keep a careful chart of (1) the apex heart rate and the pulse deficit (difference between apex and radial pulse rates) especially if there is atrial fibrillation (2) the loss of weight and urine output (as compared to fluid intake) to note a diuretic action and (3) subjective symptoms of improvement (Figure 151 page 829) The vital

capacity record may also prove of interest rising with decrease in the degree of failure. And finally the *T* wave of the electrocardiogram often but not always shows changes characteristic of the effect of digitalis becoming biphasic and flattened at first especially in its early part (or more exactly the *ST* segment) and eventually with full digitalization becoming deeply inverted (Chapter 9 and Figure 152). When the ventricular rate is high in atrial fibrillation intravenous strophanthin or rapid digitalization usually causes a sharp drop in rate in the course of an hour or two finally in a few hours there may be complete disappearance of pulse deficit (with even a slight rise of radial pulse rate in rare cases if such radial pulse rate was at first low because of weakness of many of the heartbeats). Along with this remarkable fall in heart rate due to the production of block in atrial fibrillation the electrocardiogram usually shows a rapid change (inversion) in the character of the *ST* segment especially in Lead 2. The diuresis that frequently results from digitalis therapy in edematous cases which incidentally was the finding that first called attention to the value of foxglove in heart disease is not the direct effect of the drug but the indirect effect of improvement of the circulation. In the absence of edema digitalis has no diuretic effect.

9 *Miscellaneous drugs without digitalis like action* Finally before leaving the discussion of digitalis and other members of the digitalis group mention should be made of certain unrelated drugs which have been occasionally substituted for or used in addition to digitalis in the treatment of congestive heart failure because of their supposed stimulating effect on the heart. None of these drugs with one exception has been shown in any way valuable because of a direct effect on the heart. The exception *epinephrine* or *adrenaline* has a powerful but transient action. It has not been found valuable in the treatment of congestive failure. At present its chief value rests in the revival of the heartbeat in standstill of the heart whether because of sinoatrial depression or of high grade atrioventricular block (Morgagni Adams Stokes attacks) it is of less value in the treatment of collapse or shock. It sometimes helps a little in a secondary role in the therapy of an attack of cardiac asthma. A recently introduced drug allied to epinephrine in action but much more gradual and persistent in effect is *ephedrine* (from the Chinese plant *ma huang*) its action in congestive failure is not favorable enough to consider its use even as an extra aid.

All other so-called stimulants if active at all produce an effect not directly on the heart but on the nervous system blood vessels or other tissues none of them can in any way take the place of digitalis. These drugs include strychnine camphor caffeine theobromine and theophylline ethylene-diamine spartein adonis vernalis physostigmine crataegus Cardiazol Coramine aconite and cactus. Caffeine has an important stimulating effect on the nervous system and vasomotor center while Coramine and theophylline ethylene-diamine (aminophylline) often stimulate and regulate a depressed respiratory center and the latter aminophylline dilates the coronary arteries and dissipates distressing Cheyne Stokes breathing and the asthmatic dyspnea in acute pul-

monary edema but they do not so far as we know have a direct myocardial action. Cactus is apparently inert.

**C Use of diuretics** When dyspnea (from pulmonary congestion) and edema in congestive heart failure are not quickly relieved by rest by the effect of digitalis or by diet and fluid restriction they usually yield to the primary diuretic properties of certain drugs. At times such diuretic drugs are of great importance in maintaining comfort and prolonging life when there is congestive failure. They should be supplementary to and not replace digitalis except perhaps in children with congestive failure secondary to acute rheumatic myocardial disease in whom digitalis is generally inert actually harmful or at least inferior to such a diuretic as theobromine sodium acetate (thesodate) (Walsh and Sprague 1941). The diuretics consists of mercury (and bismuth) compounds, purine derivatives and various salts including chlorides, nitrates and urea. The most helpful diuretic drugs which have now come into routine use are the mercurials (especially Mercuhydrin) and ammonium chloride (see below).

**1 Mercury is a powerful diuretic.** It was used for many years in the form of calomel (mercurous chloride) by mouth but in more recent years, much more satisfactory mercury compounds for intravenous or intramuscular or even oral use have been introduced. Diarrhea and stomatitis can be very disagreeable toxic effects from the oral administration of mercury although occasionally astonishing diuresis results. Following the historic use of calomel there were introduced the newer mercurial compounds Novasurol or Merbaphen (a mercury urea compound), Salyrgan or mersalyl (a mercury salicylate compound) and Mercupurin or novurit (a mercury theophylline compound) which were given intravenously or intramuscularly in the initial dose of 1 to 2 cc (of a 10 per cent solution) and then daily or at intervals of a few days to one or two weeks or longer in the dosage of 2 cc as needed (Figure 153 opposite). The last two mentioned preparations Salyrgan and Mercupurin were more effective and less toxic than Novasurol. The most used mercurial diuretics today are Mercuhydrin (a mercury alluride compound) best given intramuscularly in the dosage of  $\frac{1}{2}$  to 2 cc, Mercuzanthin (mercuriophylline i.e. a compound with theophylline) and Thiomerin (sodium mercaptacetate) this last administered subcutaneously. These mercurials can be repeated frequently on occasion even as often as daily or every other day but it is of course best to avoid excessive dosage and to increase the interval between injections as soon as possible and as widely as possible. Also the smaller the effective dose the better. Not infrequently  $\frac{1}{4}$  to  $\frac{1}{2}$  cc may be quite adequate and not so exhausting as the larger doses of 1 to 2 cc. Care must be used to avoid serious toxic effects but such are very rare only a few deaths have been reported among hundreds of thousands of injections although true hypersensitiveness to Mercupurin has been noted (Fox, Gold and Leon 1942). Sodium mercaptacetate (Thiomerin) has the added convenience of subcutaneous administration which makes it possible for personal use by the patient himself or by one of his family.

These mercurial preparations may be used with some success even for ascites due to cirrhosis of the liver. Extraordinarily large amounts of these drugs have been given to a single patient with constant benefit and apparently no harm whatsoever to kidneys, liver or other organs for example 240 cc of Salyrgan in 198 doses to one patient (Maxwell Scott and Harvey 1933) and 270 injections over a period of five years to another (Wiseman 1932). The simultaneous administration of various ammonium or other such salts by mouth often reinforces and increases the diuretic action of the mercury preparations but if they are active themselves there may be no need of giving these other drugs. Mercury may be given by suppository also in the form of Mercurin or Mercupurin but it is less effective and often irritating.

2 Bismuth and arsenic though possessing some diuretic properties are inferior to mercury in the treatment of obstinate edema.

3 Of the purine group caffeine itself is too weak to be particularly useful. Theobromine or theobromine sodium salicylate (Diuretin) is one of the most

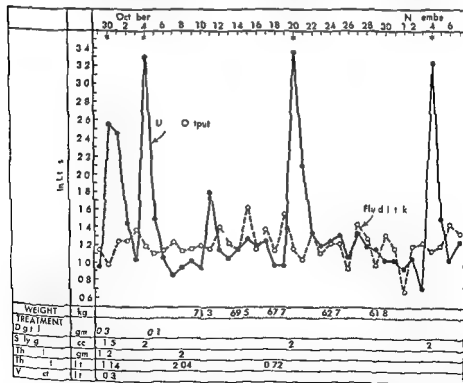


FIG 153 Chart showing the effect of the diuretic therapy of congestive heart failure in an elderly man. There is especially evident the vigorous action of the mercury preparation Salyrgan (mersalyl) injected intravenously. Life was prolonged in relative comfort and quiet activity for about one year in the case of this patient by the occasional use of Salyrgan. Digitalization alone with its constant maintenance was inadequate.

Me. uhyd in Mercupurin and Thiomerin may now be used in preference to Salyrgan. (See text.)

valuable diuretics because it is often effective and but slightly toxic. It is best given in the dosage of 0.5 to 1.0 gm ( $7\frac{1}{2}$  to 15 gr) of the salt or 0.5 gm ( $7\frac{1}{2}$  gr) of the alkaloid in powder or tablet form three times a day for several days or weeks. If effective it may be kept up constantly or it may be discontinued after an interval and then resumed again in repeated courses later for several days at a time for example every ten days or two weeks as needed. *Theocalcin* (theobromine calcium salicylate)  $7\frac{1}{2}$  gr tablets or *Thesodate* (theobromine sodium acetate) in enteric coated tablets of  $3\frac{3}{4}$  to  $7\frac{1}{2}$  gr or *Glucophylline* (double salt of theophylline 1.18 gr and methylglucamine 1.16 gr) may be given in the place of Diuretin. In half of the cases of obstinate edema not yielding to rest and digitalis theobromine or one of its salts suffices. But for other cases more vigorous diuretics are necessary. These include other of the purines theophylline (or Theocin) and its derivative theophylline ethylene diamine (aminophylline) or Phyllicin which may be also given for several days trial. If effective they may be resumed for intervals of a week or two as needed. Either of these drugs theophylline or its derivative may be administered as small daily rations in 3 gr doses three times a day but they are more likely to upset the digestive tract than are the theobromine compounds. A more or less constant mild diuresis may be maintained by the use of drugs of the purine group given by mouth.

The chief difficulty in the use of either theobromine or theophylline especially of the latter is that these drugs are very likely to produce toxic symptoms chiefly nausea and vomiting but their various salts are much better borne. It may be added that theobromine and allied drugs have been given in the treatment of coronary insufficiency and Cheyne Stokes respiration sometimes with great benefit. theophylline ethylene diamine (Metaphyllin or aminophylline) has been particularly effective in the control of Cheyne Stokes respiration given intravenously in the dosage of 0.25 gm (4 gr)—it is always worth trying and sometimes smooths out the breathing within a minute or two.

4. Certain salts namely ammonium chloride ammonium nitrate ammonium sulfate magnesium sulfate calcium chloride and urea also have diuretic properties especially the ammonium salts associated with their production of a mild acidosis and resultant extraction of sodium from the body. When given alone they may or may not be sufficiently active. In order to produce an effect by themselves they have to be administered sometimes in large doses (for example 8 to 10 gm of ammonium chloride daily) and they are generally disagreeable to take. As an adjuvant to mercury compounds in the treatment of obstinate edema ammonium chloride or ammonium nitrate is often helpful in the dose of 1.0 to 1.5 gm (15 to  $22\frac{1}{2}$  gr) four times daily. The ammonium salt should be given in enteric-coated pills of  $7\frac{1}{4}$  gr (0.5 gm) each. Urea may be given for weeks or months effectively in the dosage of 10 to 25 gm two or three times a day in a 40 per cent watery solution but it is not so useful. Often these salts are not necessary the mercury alone proving adequate but occasionally they are quite effective and worthy of trial when the mercurial therapy is insufficient, and in some cases they may be used alone.

with beneficial mild diuresis. Calcium (and potassium) salts (for example calcium gluconate) in high dosage should not be administered to digitalized patients because of the hazard of serious toxic effects on the cardiac mechanism.

5 Finally *parathyroid extract* (*parathormone*) has been found to have diuretic properties. Although it mobilizes calcium in the blood it acts differently from calcium chloride which causes diuresis by producing an acidosis. Parathormone has not however been used clinically to replace the other diuretics.

The exact mechanism of the action of primary diuretic drugs is not always clear. It apparently is chiefly through the effect of the drugs on the glomeruli (punnies) and tubules (mercury derivatives) of the kidneys, whether the drugs act also through some process that controls the water content of the tissues themselves is not known.

D **Other drug therapy** Although drug therapy other than that directed toward rest and stimulation of the heart by digitalis and allied drugs and that concerned with diuresis has only a secondary place in congestive heart failure, important effects are occasionally secured which mean the difference between success and failure in a given case.

1 The *narcotics sedatives and hypnotics* are the most important of these other drugs. For acute paroxysmal dyspnea (pulmonary edema) with or without cardiac asthma, morphine sulfate 0.015 gm ( $\frac{1}{4}$  gr) subcutaneously at the onset of the attack has a striking effect to quiet the patient, improve the breathing and shorten the attack. Also at times a dose of morphine given to a greatly distressed patient with congestive failure who has been unable to sleep and has been uncomfortable for days may bring the first rest and peace of mind and start the patient on the road to recovery. Morphine should of course be avoided by omitting the drug as soon as possible. Atropine sulfate 0.6 mg ( $\frac{1}{100}$  gr) may be given with the morphine to reduce the nausea from its vagal effect as well as to reduce secretions. Pantopon in the dosage of 0.02 gm ( $\frac{1}{2}$  gr) or Dilaudid 0.002 gm ( $\frac{1}{32}$  gr) may be tolerated better and have as effective therapeutic action as morphine in some patients. Even codeine sulfate may on occasion be used effectively in the dosage of 0.03 to 0.06 gm ( $\frac{1}{2}$  to 1 gr) subcutaneously or by mouth in the place of morphine which has more disagreeable after-effects. Bromides, whisky or brandy and the hypnotics (of many kinds) also have a place in certain cases bothered by headache, worry and sleeplessness. Narcotics should be generally omitted when there is distressing Cheyne Stokes respiration. When phenobarbital and allied hypnotics are ineffective or actually disturbing in their action and morphine is not applicable, a very useful and safe drug to control insomnia and great restlessness is paraldehyde given by mouth, rectum or intramuscularly in the dosage of 11 to 16 cc (2 to 4 drachms) to be repeated as needed.

2 *Oxygen inhalation* (50 to 100 per cent oxygen by special mask or in special tent or chamber or by naso- or oropharyngeal insufflation) has an important place in combating dyspnea and cyanosis in acute congestive failure.



and in tiding cardiac patients over important complications especially pulmonary infection and infarction and although not suitable for constant use in chronic failure it may be helpful in daily rations in the case of patients with persistent congestion of the lungs. The introduction of the gas helium in the place of air as the diluent of the oxygen helped very materially in reducing respiratory effort in the inhalation of oxygen (Barach 1934) but helium leaks easily and has been expensive and difficult to obtain especially in wartime.

3 In many cases of congestive heart failure or very limited myocardial reserve in which the diet is inadequate or absorption of food elements defective sometimes because of the disease itself and sometimes because of the effect of drugs it is essential to administer *vitamins*. Such therapy in milder cases may be by mouth in the form of (a) vitamin B complex which contains thiamine, nicotinic acid and riboflavin in amounts sufficient to combat beriberi, pellagra and dermatoses (b) orange juice to combat scurvy and when necessary (c) vitamins A and D. In severe cases with evident avitaminosis usually multiple it may be necessary to give vitamins parenterally for example thiamine HCl 50 to 100 mg daily, nicotinic acid 50 to 80 mg and ascorbic acid 50 to 150 mg or more if needed urgently for actual scurvy (up to 1 200 mg in the first dose).

4 The *cathartics and laxatives* are often indispensable. Half an ounce of magnesium sulfate every day or every other day may yield one or two watery stools which help not only to keep the bowels open but to get rid of edema. Other cathartics may also be used avoiding those containing sodium. Senna in the form of a simple aqueous extract of the pods is often a mild but effective laxative. Vigorous purgation is to be strongly deprecated because of its weakening effect which is in part due to the repeated need of going to stool when absolute rest would be far better for the patient and in part due to the nausea that may be induced.

5 The *drug treatment of other diseases* like syphilis which complicate congestive heart failure must be carried out with the greatest of care if at all. Generally it is wise to omit all such treatment until the heart has regained its strength.

6 Symptomatic treatment of headache, indigestion and other functional disorders may be carried out as in the absence of heart failure except that drugs containing sodium should not be given except in very small doses. Various other preparations that have been given in the past for supposedly specific myocardial action like dextrose (glucose) intravenously have been largely abandoned.

E *Diet, salt and fluid intake*. Diet regulation is an important part of the treatment of congestive failure. Much has been written on this subject in the past but practically all the information afforded has been empirical based on personal or vague opinions about specific foods and fluid intake. General advice has been given to restrict the diet to simple food relatively light in caloric value and in bulk with some restriction of fluids and salt. Although this advice has been effective for generations in the case of individuals with heart disease without severe involvement in the form of myocardial or coronary insufficiency many cases have needed better detailed advice. Fortunately

during the last five to ten years such advice has come and although we are not yet at the end of the story we can be much more specific and helpful especially in the case of myocardial insufficiency and congestive heart failure

In the first place the most important item of all is the *restriction of sodium* to a reasonably low level sometimes to an extremely low level temporarily to help clear congestion The specific value of the restriction of sodium chloride in the control of congestion was first clearly pointed out by Widal and Lemierre in 1903 and by Strauss in 1908 \* It is the sodium that holds water in the body and hence the less sodium intake or the greater the sodium output the less water is held in the body with less congestion and the more comfortable is the patient There is a limit to sodium restriction however and sometimes there are unfortunate results in the form of salt lack Therefore it is possible to overdo this very helpful therapy of limited salt intake

Salt that is sodium chloride should be fairly accurately measured in the food and there are tables now listing the sodium content of many foods The reader is referred to one special list as follows Sodium and Potassium Analyses of Foods and Waters Fifth List October 1947 With Additions and Corrections Mead Johnson & Company Evansville 21 Indiana The sodium chloride content of the usual diet varies greatly according to individual liking and habit There is a range from about 5 to 15 or more grams per day 8 to 10 being very common A simple reduction to 3 or 4 gm a day may suffice to help keep congestion under control Sometimes however a stricter reduction is necessary to 1 or 2 gm a day and on occasion a stricter reduction is to less than 1 gm which would give an actual sodium level of less than  $\frac{1}{2}$  gm Such is found in certain diets like the rice diet of Kempner Control testing of the amount of sodium taken in can be gauged by the measurement of the chlorides in the urine Strict sodium restriction can be carried out for a good many weeks or months and in less severe form for years but there should be frequent appraisal of the details of the diet in each case Various salt substitutes have been introduced to make more palatable the low sodium diets unfortunately the best containing lithium chloride was used too freely and resulted in lithium poisoning in some cases but in small dosage (a few drops at each meal) it may still be taken to advantage

An ingenious method for limiting the sodium content of the body has been the administration of resinous compounds which attract and hold electrolytes in particular sodium in the gastrointestinal contents (too great a depletion of other electrolytes especially of potassium is avoided) various preparations of resin although not yet perfected and difficult for some patients to take have permitted the ingestion of more palatable food and longer time intervals between mercurial injections in suitable cases of obstinate congestive heart failure (Dock 1946 1950)

The next important item about the food and fluids concerns the caloric

\* It is of interest that John of Gaddesden in his famous book (*Rosa angl a practica medicinae a capite ad pedes* printed by Johannes Antonius in Treva Pavia 149-) refers to the value of limiting the salt content of the diet in cases of dropsy His work was in manuscript at the time of Chaucer in the middle of the fourteenth century 500 hundred years ago

value This should be adequate to maintain nutrition and yet low enough to allow loss of weight if there is obesity Sometimes four or five small meals a day are more readily tolerated than two or three larger ones especially in the case of a severely ill patient Not infrequently the old Karell diet (cure de lait) can be used for a day or two with benefit This consists of 800 cc of skimmed milk divided into four portions during twenty four hours This is a starvation diet with restriction of salt and limitation of metabolic needs for digestion which may help to start treatment in the case of a severely congested patient It is not to be used as a rule for more than a day or two at a time In some diets such as that of the rice diet the protein intake is very low This is generally not necessary It is usually best to give protein intake enough to keep a normal nitrogen balance—1 gm per kilogram of body weight is usually satisfactory If there is much loss of albumin by the urine in the complicated case, more protein may be added to the food It is generally best to keep all fats low and to supply most of the calories by carbohydrates

Finally as to fluid intake formerly and for centuries as a matter of fact there was great restriction of fluid intake with unhappy results The patient was often rendered very miserable and constantly thirsty by the reduction of fluids to one liter or less in twenty four hours Now we have come to realize belatedly that adequate fluids should be administered usually best in the amount of about 2 to 3 liters in twenty four hours and in rare cases even more if the kidney status demands such for adequate ridding of the blood of impurities Only infrequently is it necessary to force fluids Most patients do well with fluid intake varying from  $1\frac{1}{2}$  to  $2\frac{1}{2}$  or 3 liters

In order adequately to control the fluid intake charts of 24 hour intake and output should be carefully kept during the period of congestive failure and for a few weeks thereafter, also so far as possible a daily weight chart should be kept for often the very first indication of the onset or recurrence of edema is an otherwise unexplained rapid gain in weight

Vitamins (see page 840) and adequate protein (a minimum of 1 gm per kilogram daily for average sized adults amounting to 60 to 70 gm in 24 hours) should be carefully included in the diet in order to maintain as good general health as possible and to prevent complications of avitaminosis and hypoproteinemia which may themselves cause heart trouble and edema although such complications are not as a rule at all prominent and in severe degree are uncommon yet they may on occasion be a cause for obstinate edema

**F Various mechanical therapeutic measures** 1 *Venesection* is rarely necessary in the treatment of congestive heart failure, but sometimes as an emergency measure it gives relief and saves lives It was much more often necessary in the days before there was a proper appreciation of how to give digitalis, that is before the time of more or less universal digitalization and maintenance of digitalis effect and also before adequate mercurial diuresis and restriction of sodium intake Venesection is applicable to two types of patients first and chiefly the cardiac patient with acute and fulminating congestive failure as in cases of pulmonary edema and of marked venous congestion, and second

rarely the chronic plethoric non nephritic hypertensive cardiac patient who tends to have obstinate or readily recurrent edema and persistently high venous pressure (over 20 cm of water in arm vein) in spite of rest digitalis diuretics and other therapy. Blood should be removed from arm vein by knife or needle in amounts between 250 and 500 cc (1/2 to 1 pt). The procedure may be repeated if needed but it should not be done unless the venous pressure is elevated and it should not be the first treatment of choice.

Another way by which temporarily the heart may be relieved of excess blood especially helpful in acute failure with pulmonary edema is constriction of the proximal parts of three extremities at a time by blood pressure cuffs or similar bands cutting off temporarily the venous circulation and so sidetracking much blood. Each extremity should be released in turn for fifteen minutes at a time. This procedure should however be used as little as possible because of the hazard of causing phlebothrombosis in the legs with resulting pulmonary embolism.

2 When rest digitalis diuretics and other measures fail to relieve ascites or hydrothorax and oppression from the fluid is disagreeable *paracentesis* should be done and as much fluid as possible withdrawn from peritoneal or pleural cavities without exhausting the patient. This is especially important in the case of hydrothorax because of the greater embarrassment of the already difficult breathing by the reduction of the vital capacity by the pleural fluid and because fluid is absorbed more slowly from the pleural than from the peritoneal cavity. It is best to use local anesthesia with 0.5 to 1 per cent procaine (novocaine) before the trocar is inserted.

3 For obstinate massive edema of the legs a condition far less common than a decade or two ago an incision 3 in. long in the dorsum of each foot or multiple punctures of the skin of each calf may be made to drain off as much fluid as possible aseptically into dressings or sterile jars or pans but a method much to be preferred is the use of *Southey's tubes* (Southey 1877) small cannulas which may be inserted into the feet or legs by means of trocars two or three on each side with rubber tubes to carry off the edema fluid which can thus be measured (Figure 150 page 820). Curschmann's tubes are less desirable than Southey's tubes in the treatment of obstinate edema because of their larger size. It is best to have the patient in the sitting position preferably in a special chair bed to get the full benefit from this procedure. Sometimes enormous quantities of fluid can be drained off by the Southey's tubes even as much as 6 liters in twenty four hours or 15 liters (about 30 pounds) in three or four days. Painful massive edema of the scrotum which is not relieved by the insertion of the Southey's tubes in the legs may be largely removed by putting one of the tubes directly into the scrotum itself as much as a liter of fluid can be drained from the scrotum in this way in a day or two. The utilization of these mechanical drainage measures is best reserved however for cases of obstinate edema which are not relieved in other ways. Infection in such patients can be prevented by the use of penicillin parenterally while the tubes are in use. As indicated above the need of such treatment has been

steadily growing rarer with improvement of our other therapeutic measures cardiac patients still fail and die but as a rule they die dry—we no longer see much anasarca today

4 The method of treatment a type of cardiolysis in reality a *thoracolysis* or *rib resection* (*precordial thoracotomy*) designed to afford mechanical relief to an embarrassed circulation in which heart failure is threatened or has actually begun which was mentioned in previous editions of this book has been rarely carried out so far as I am aware It is similar to the equally rare operative procedure introduced to give relief to the heart when it is tied to the chest wall by pericardial adhesions (Brauer's operation; Brauer 1902) Several ribs and costal cartilages usually the fourth fifth and sixth of the left anterior chest wall are removed in this operation in order to give more freedom to a very large heart pounding against a rather rigid barrier The operation was apparently beneficial in a few cases chiefly by relief of subjective discomfort (palpitation and precordial ache), but it must still be considered as an experimental measure and not likely to be helpful in many cases It has been developed further in the last fourteen years since the publication of the second edition of this book but it must be realized that there results from this procedure an undesirable deformity of the thorax interfering with the mechanism of respiration

5 *Total thyroidectomy* in the treatment of congestive heart failure and angina pectoris was an extremely interesting innovation years ago (Blumgart Levine and Berlin 1933) It had been observed that a cardiac patient thought to have thyroid disease improved considerably for a period of time after the subtotal removal of a normal thyroid gland this was the forerunner of the idea that was finally put into execution that total ablation might dissipate congestive heart failure and angina pectoris by its effect in reducing markedly the basal metabolic rate and so cutting down the demands on the myocardium and coronary circulation This idea proved true and the operation became for a few years established as one of the radical measures of cardiac treatment that seemed suitable in about 1 per cent of the patients routinely seen for congestive failure or angina pectoris Both successes and failures were reported in the application of this treatment Almost all of the early enthusiasm has waned and yet there remained a place for this idea and recently it has evolved into a medical thyroidectomy for obstinate myocardial or coronary insufficiency by the ingenious use of irradiated iodine I 131 (Blumgart and Freedberg 1948) Minute amounts of this preparation are given by mouth over a period of 2 or 3 weeks in order to introduce from 25 to 100 millicuries into the body a considerable proportion of which settles in the thyroid gland where the cells are exposed to the radiation In the course of 4 to 8 weeks the metabolic rate is reduced sufficiently to afford relief of symptoms in most cases A high degree of myxedema is prevented by the administration of small doses of thyroid

Other surgical operations such as appendectomy to correct serious lesions in the presence of congestive heart failure should be limited to emergencies and so far as possible some preparation by rapid digitalization should be

carried out first if there is inadequate digitalis therapy already. Thyroidectomy for thyrotoxicosis is however one operation which is as a rule indicated rather than contraindicated. This surgical measure may actually abolish the congestive heart failure. In cases of prostatic obstruction also it may be difficult to restore or to hold myocardial competency until the patient has been put on constant bladder drainage and submitted later to a transurethral prostatectomy. In any of these surgical procedures the greatest care must be taken in securing the best anesthesia possible (see Chapter 23).

**6 Physical therapy** Special measures of physical therapy—exercises, massage, baths, electrotherapy—have little place in the treatment of congestive failure except for massage of arms and legs which may be useful in helping to maintain the peripheral circulation and so to prevent phlebothrombosis, the precursor of pulmonary embolism, and gentle passive or active exercises during convalescence but not while there is still dyspnea or edema. Other measures such as carbon dioxide baths and more vigorous exercises are to be prescribed only after the congestive failure has cleared up to help to improve the general circulation and thereby to increase the cardiac reserve.

**G Environment and other factors** Finally it is important to remember that a patient may be overtreated and hastened to his end by the too zealous simultaneous application of a number of measures, each one of which may be valuable in itself when applied with common sense. A patient who at home is in a chronic state of slight to moderate but not dangerous congestive failure may be brought for treatment to a hospital where in a new and strange environment he is bled, purged, much restricted as to food and fluids, and given a number of potent drugs. Unable to stand the strain of so much effective therapy, he may die within a few days. *Good judgment* must be well mixed with all the rest of the treatment of such a sick patient as the one with congestive heart failure. Health resorts a long way from the patient's home are far less suitable for his care during severe congestive failure than are hospitals near at hand or the patient's own home itself. During convalescence the change of scene and divers interests at some well-conducted sanitarium or spa may justify the patient's journey thither, but good medical supervision should be a requisite; the patient should not return home a wreck as has sometimes happened. Also during convalescence it is worthwhile to prescribe not only graded exercise but some interest like music, art, science, history, literature, or even stamp collecting, as well. Last but not least is the *spirit of cheerfulness* that should surround the patient, a natural attribute of a good doctor and a good nurse and one of the chief elements in the psychotherapy of heart disease.

**Differential diagnosis** Congestive heart failure must be differentiated from neurocirculatory asthenia, from the effect of obesity and poor physical training on the respiratory reserve, and from nephritis, starvation, peritonitis, cirrhosis of the liver, malignant disease, constrictive pericarditis (acute or chronic), and infections which may cause edema, ascites, hepatic enlargement, hydrothorax, and rales in the lungs. The diagnosis of congestive heart failure is generally readily made by finding the combination of serious organic

heart disease dyspnea or dependent edema and a favorable response to digitalis therapy. It is particularly important on rare occasions to distinguish acute pulmonary edema due to left ventricular failure or to mitral stenosis from that of so called neurogenic origin (see page 63 Chapter 4)

There are two conditions that are particularly likely to be confused with the results of myocardial failure one very common namely *pulmonary disease* and the other rare acute or chronic *constrictive pericarditis*. Careful history and physical examination as a rule prevent errors. Pulmonary symptoms and signs are not due to heart disease unless there is evidence of that disease in the form of cardiac enlargement murmurs of valvular deformity or important myocardial infarction the main difficulty is in determining the relative responsibility in producing symptoms and signs when both heart disease and pulmonary disease are present in the same patient. Acute or chronic constrictive pericarditis causes all the evidences of congestion in the systemic veins liver and dependent parts of the body that are caused by myocardial failure but the heart itself is usually but little involved in the case of constrictive pericarditis except for a rather characteristic electrocardiogram and sometimes a slightly enlarged x ray heart shadow, and there is a history usually in a young person of the gradual development of dropsy especially a big liver and ascites without adequate heart trouble to account for it and unaided by digitalis therapy in a few cases an acute pericarditis precedes the chronic trouble (see Chapter 27)

## BIBLIOGRAPHY

### MYOCARDIAL INSUFFICIENCY AND CONGESTIVE HEART FAILURE

SEE ALSO GENERAL REFERENCES FOLLOWING CHAPTER 2 AND REFERENCES UNDER DYSPNEA AND CARDIAC ASTHMA IN CHAPTER 3 CYANOSIS EDEMA AND ASCITES IN CHAPTER 4 GALLOP RHYTHM IN CHAPTER 5 AND BASAL METABOLIC RATE DETERMINATIONS FUNCTIONAL TESTS BLOOD FLOW AND CIRCULATION RATE STUDIES IN CHAPTER 10

- Altschule M H "The Pathological Physiology of Chronic Cardiac Decompensation" *Melinc* 1938 XVII 75
- Assmann H "Über Veränderungen der Hilusschatten bei Herzkrankheiten" *Munch med Wchnschr* 1920 LXVII 28
- Austrian C R "Encapsulated Hydrothorax (Hydrothorax Saccatus Interlobans) in Association with Myocardial Insufficiency" *Likman Anniversary Volumes* 1931 101
- Baer S., and Isard H J "The Value of the Ether Circulation Time in the Diagnosis of Right Heart Failure" *Am J M Sc* 1940 CC 209
- Bernheim "De l'asthysie veineuse dans l'hypertrophie du coeur gauche par stenose concomitante du ventricule droit" *Rev de Med* 1910 XXX 785
- Boland F W and Willis F A "Changes in the Liver Produced by Chronic Passive Congestion with Special Reference to the Problem of Cardiac Cirrhosis" *Arch Int Med* 1938 LXII 723
- Boyer N H Leach C F and White H D "Underlying Causes and Precipitating

- Factors of Congestive Heart Failure *Pub 13 Am A Advancement Sc* 1940 II 203  
 "The Immediate Prognosis of Congestive Heart Failure" *Ann Int Med* 1941  
 XIV 2210
- Boyer N H and White P D "Right Upper Quadrant Pain on Effort An Early  
 Symptom of Failure of the Right Ventricle" *New England J Med* 1947 CCXXVI  
 217
- Clawson II J "The Myocardium in Non Infectious Myocardial Failure" *Am J M Sc*  
 1974 CLXVIII 648
- Dock W "The Anatomical and Hydrostatic Basis of Orthopnea and of Right Hydro  
 thorax in Cardiac Failure" *Am Heart J* 1935 X 1047
- Dwyer M F and Carille T "Localized Interlobar Collection of Fluid in Congestive  
 Cardiac Failure" *Clin Virginia Mason Hosp* 1943 XXII 11
- East T *Failure of the Heart and Circulation* Staples Press London 2nd ed 1948 (John  
 Bale Sons and Curnow Ltd London 1st ed 1937)
- Fahr G and Ershler I "Studies of the Factors Concerned in Edema Formation II  
 The Hydrostatic Pressure in the Capillaries during Edema Formation in Right Heart  
 Failure" *Ann Int Med* 1941 XV 798
- Futcher P H and Schroeder H A "The Impaired Renal Excretion of Salt in Chronic  
 Congestive Heart Failure" *Soc Proc J Clin Investigation* 1941 XX 458
- Gravier L *Alternance du coeur Etude critique et clinique* J B Bailliere et fils  
 Paris 1914
- Gross H "Water Content of Myocardium in Hypertrophy and Chronic Congestive  
 Failure" *J Lab & Clin Med* 1940 XXV 899
- Gross H and Handler B J "Sclerosis of Superior Vena Cava in Chronic Congestive  
 Heart Failure" *Arch Path* 1939 XXVIII 72
- Hamburger W W Katz L N and Saphir O "Electrical Alternans A Clinical Study  
 with a Report of Two Necropsies" *JAMA* 1936 CVI 902
- Harrison T R *Failure of the Circulation* Williams and Wilkins Co Baltimore  
 2nd ed 1939 (1st ed 1935)
- Hitzig W M King F H and Fishberg A M "Circulation Time in Failure of Left  
 Side of Heart" *Arch Int Med* 1935 LV 112
- Hope J A *Treatise on the Diseases of the Heart and Great Vessels* William Kidd  
 London 1832
- Katzin H M Waller J V and Blumgart H L "Cardiac Carcinosis of Liver  
 Clinical and Pathologic Study" *Arch Int Med* 1939 LXIV 457
- Kinsey D and White P D "Fever in Congestive Heart Failure" *Arch Int Med*  
 1940 LXV 163
- Lancini J M *De Motu Cordis et Aneurysmatibus* J M Salvioni Rome 1778
- Leech C B "An Improvement of Southey's Tubes" *JAMA* 1936 CVI 1895
- Lewis T "Bedstead for Use in Treating Cardiac Patients Suffering from Congestive  
 Failure" *Brit M J* 1928 II 977
- Lian C *Le syndrome d'insuffisance ventriculaire gauche* *Presse med* 1910 XVIII 49
- Mackenzie J *Diseases of the Heart* Henry Frowde Hodder and Stoughton Oxford  
 University Press 3rd ed 1913 (1st ed 1908)
- Meneely G R and Kaltreider N L "A Study of the Volume of the Blood in Con  
 gestive Heart Failure" *J Clin Investigation* 1943 XXII 521
- Meyer A "Die akute Herzdilatation" *Klin Wchnschr* 1934 XIII 758
- Myers V C "Some Chemical Changes in the Myocardium Accompanying Heart Failure"  
*Bull New York Acad Med* 1942 XVIII 301
- Nessa C B and Rigler L G "Rontgenologic Manifestations of Pulmonary Edema"  
*Radiology* 1941 XXXVII 35
- Proger S Ginsburg E and Magendantz H "The Effects of the Ingestion of Ex  
 cessive Amounts of Sodium Chloride and Water on Patients with Heart Disease"  
*Am Heart J* 1947 XXIII 555
- Redfield A C and Medearis D N "The Content of Lactic Acid and the Develop  
 ment of Tension in Cardiac Muscle" *Am J Physiol* 1926 LXXVII 662
- Richards II W Jr and associates "Pressure in the Right Auricle of Man in Normal  
 Subjects and in Patients with Congestive Heart Failure" *Tr A Am Physicians* 1941  
 LVI 218



- Seymour W B and associates Cardiac Output Blood and Interstitial Fluid Volumes Total Circulating Serum Protein and Kidney Function During Cardiac Failure and After Improvement *J Clin Investigation* 1942 XXI 229
- Sharpey Schafer E P and Wallace J Circulatory Overloading Following Rapid Intravenous Injections *Brit M J* 1942 II 304
- Sodeman W A and Burch G E The Precipitating Causes of Congestive Heart Failure *Am Heart J* 1938 XV 22
- Sotialo P Über Stauungshypertonie *Acta Soc Med Fennicae Duodecim* Helsinki 1939 XXVII Ser B Fasc 1-2
- Stewart H J and associates The Cardiac Output in Congestive Heart Failure and in Organic Heart Disease *Ann Int Med* 1940 XIII 2323
- Thompson W H and White P D The Commonest Cause of Right Ventricular Hypertrophy Weakness and Failure of the Left Ventricle *Am Heart J* 1936 XII 641
- Traube L Ein Fall von Pulsus bigeminus nebst Bemerkungen über Arteriosclerose über Leberschwellungen bei Klappenfehlern und über acute Leberatrophie *Berlin klin Wchnschr* 1872 IX 185 and 221
- Vieussens R *Traité Nouveau de la Structure et des Causes du Mouvement naturel du Cœur* Jean Guillemette Toulouse 1715
- Volhard F Ueber den Pulsus alternans und pseudoalternans *Munch med Wchnschr* 1905 LII 590
- Walsh B J and Sprague H B Character of Congestive Failure in Children with Active Rheumatic Fever *Am J Dis Child* 1941 LXI 1003
- Wassermann S Das akute kardiale Lungenodem und sein reflektorischer Mechanismus Pathogenese Pathophysiologie (Symptomatologie) Differentialdiagnose und Therapie *Wien Arch f inn Med* 1933 XXIV 213
- Welch W H Zur Pathologie des Lungenodems *Virch Arch f path Anat* 1878 LXXII 375
- White P D Alternation of the Pulse A Common Clinical Condition *Am J M Sc* 1915 CL 87
- Weakness and Failure of the Left Ventricle Without Failure of the Right Ventricle Clinical Recognition *JAMA* 1933 C 1993
- Heart Failure *Bull New York Acad Med* 1942 XVIII 18

#### Recent References (1944-1950)

- Benton J G Brown H and Rusk H A "Energy Expended by Patients on the Bedpan and Bedside Commode" *JAMA* 1950 CXLIV 1443
- Boharas S and Crip L H Interlobar Effusion Associated with Congestive Heart Failure" *Ann Int Med* 1945 XXIII 426
- Briggs A P Fowell D M Hamilton W F Remington J W Wheeler N C and Winslow J A "Renal and Circulatory Factors in the Edema Formation of Congestive Heart Failure" *J Clin Investigation* 1948 XXVII 810
- Burch G E "Disturbances of Water and Sodium Balance in Congestive Heart Failure" *Med Concepts Cardiovas Dis* 1948 XVII No 5
- Currens J H and White P D "Congestive Heart Failure and Electrocardiographic Abnormalities Resulting from Excessive Desoxycorticosterone Acetate Therapy in the Treatment of Addison's Disease" *Am Heart J* 1944 XXVIII 611
- "Great Reduction in Heart Size Attending the Clearing of Congestive Heart Failure in a Man with Hypertensive and Coronary Heart Disease" *Ann Int Med* 1949 XXXI 912
- Dalton C J Darling R C and Shea E "The Insensible Loss of Water in Congestive Heart Failure" *Am J M Sc* 1948 CCXVI 516
- DiMaio M "Multiple Localized Pleural Effusions as a Manifestation of Congestive Heart Failure" *New England J Med* 1948 CCXXVIII 502
- Evans L R., and White P D "Massive Hypertrophy of the Heart with Special Reference to Bernheim's Syndrome" *Am J M Sc* 1948 CCXVI 485
- Fleischner F G and Udis S W "The Width of the Azygos Vein—A Roentgen Sign of Venous Engorgement" *Proc New England Cardiovas Soc* 1949-50 p 41
- Fox, C L., Jr Friedburg C K and White A G Electrolyte Abnormalities in

- Chronic Congestive Heart Failure Effects of Administration of Potassium and Sodium Salts *J Clin Investigation* 1949 XXVIII 781
- Gelfer W I Boucot K R and Marshall E W "Localized Interlobar Effusion in Congestive Heart Failure Vanishing Tumor of the Lung" *Circulation* 1950 II 336
- Huckabee W Casten G and Harrison T R "Experimental Hypervolemic Heart Failure Its Bearing on Certain General Principles of Heart Failure" *Circulation* 1950 I 343
- Leiter L "The Role and Control of Renal Dysfunction in Congestive Heart Failure" *New York State J Med* 1948 XLVIII 1803
- Lenegre J and Minkowski A "L'œdème aigu et subaigu du poumon. Constatations cliniques, radiologiques, pathologiques et thérapeutiques" *Ann de méd* 1946 XLVII 53
- Mack I Grossman M and Katz L N "The Effect of Pulmonary Congestion on Distensibility of the Lung" *Federation Proc Fed of Am Soc for Exper Biol* 1950 VI 161
- McPeak E M and Levine S A "The Preponderance of Right Hydrothorax in Congestive Heart Failure" *Ann Int Med* 1946 XXV 916
- Mangun G H and Myers V C "Cardiac Muscle Further Studies Investigation of Chemical Changes in Myocardial Insufficiency with Special Reference to Adenosine triphosphate" *Arch Int Med* 1946 LXXVIII 441
- Mathivat A "L'hépatalgie d'effort test d'insuffisance ventriculaire droite" *La France Médicale* 1950 XIII 9
- Mokotoff R Ross G and Leiter L "Renal Plasma Flow and Sodium Reabsorption and Excretion in Congestive Heart Failure" *J Clin Investigation* 1948 XXVII 1
- Newman W and Fishel L "Observations on the Daily Changes in Venous Pressure and Weight in a Case of Chronic Congestive Heart Failure" *Circulation* 1950 I 706
- Rader H H and Goodman H D "Congestive Heart Failure in Utero Case Report with Necropsy Findings" *J Pediatrics* 1950 XXXVI 730
- Richards D W Jr "Contributions of Right Heart Catheterization to Physiology of Congestive Heart Failure" *Am J Med* 1947 III 434
- Robertson F A "Interlobar Hydrothorax in Cardiac Failure" *Brit Heart J* 1951 XIII 117
- Ross J F Baker W H and Freis E D "The Blood Volume in Congestive Heart Failure" *J Clin Investigation* 1950 XXIX 84
- Schlesinger H "Neurogenic Pulmonary Edema Due to Puncture Wound of the Medulla Oblongata" *J Nerv & Ment Dis* 1945 CII 747
- Sherer M G and Greer W E II "Cyclic Premenstrual Congestive Heart Failure" *New England J Med* 1951 CCXLIV 973
- Sherlock S "The Liver in Heart Failure Relation of Anatomical Functional and Circulatory Changes" *Brit Heart J* 1951 XIII 273
- Starr I "Our Changing Viewpoint About Congestive Failure" *Ann Int Med* 1949 XXV 1
- Stead E A Jr "Edema of Heart Failure" *Bull New York Acad Med* 1948 XXIV 607
- Stead E A Jr Warren J V and Brannon E S "Cardiac Output in Congestive Heart Failure" *Am Heart J* 1948 XXXV 5-9
- Vakil R J "A Statistical Study of 1781 Cases of Congestive Cardiac Failure or Myocardial Insufficiency in India" *The Indian Physician* 1949 VIII 81
- Warren J V and Stead E A Jr "Fluid Dynamics in Chronic Congestive Heart Failure Interpretation of Mechanisms Producing Edema Increased Plasma Volume and Elevated Venous Pressure in Certain Patients with Prolonged Congestive Failure" *Arch Int Med* 1944 LXXIII 138
- Wheeler E O and White P D "Insomnia Due to Left Ventricular Heart Failure Unrecognized as Such and Inadequately Treated" *JAMA* 1945 CXXIX 1158
- White P D August S and Michie C R "Hydrothorax in Congestive Heart Failure" *Am J Med Sci* 1947 CCXIV 243

Digitalis Action and Therapy Strophantidin (Onabain) (See also references under Atrial Fibrillation and Atrial Flutter in Chapter 33)

- Batterman R C, Rose A and DeGraff A C "The Combined Use of Ouabain and Digitalis in the Treatment of Congestive Heart Failure" *Am Heart J* 1940 XX 443
- Bland E F and White P D "The Strength of Digitalis in Clinical Use A Warning" *JAMA* 1941 CXVII 1243
- Cattell McK and Gold H "Influence of Digitalis Glucosides on Force of Contraction of Mammalian Cardiac Muscle" *J Pharmacol & Exper Therap* 1938 LXII 116
- Chavez I "The Comparative Value of the Action of Digitalis and of Ouabain in the Treatment of Heart Failure" *Arch Int Med* 1943 LXXII 168
- Christian II A "Digitalis Therapy Satisfactory Effects in Cardiac Cases with Regular Pulse Rate" *Am J M Sc* 1919 CLVII 593
- Cohen R V and Brodsky M L "Allergy to Digitalis" *J Allergy* 1940 XII 69
- Cohn A E and Fraser F R "Certain Effects of Digitalis on the Heart" *J Pharmacol & Exper Therap* 1913-14 V 512
- Cushny A I "The Action and Uses in Medicine of Digitalis and Its Allies" Longmans, Green and Co London 1925
- Dearing W H, Barnes A R and Essex II E "Experiments with Calculated Therapeutic and Toxic Doses of Digitalis I Effects on the Myocardial Cellular Structure. II Effects on the Electrocardiogram" *Am Heart J* 1943 XXV 648 655
- Edens E "Die Digitalisbehandlung" Urban and Schwarzenberg Berlin and Vienna 1933 (2nd ed.)
- Edmunds C W "The Potency of Digitalis Preparations of the 1936 Pharmacopeia" *JAMA* 1939 CXIII 284
- Egleston C "Digitalis Dosage" *Arch Int Med* 1915 XVI 1
- Eichna L W and Taube H "A Comparison of the Actions of Four Cardiac Glycosides on a Patient with Congestive Heart Failure" *Am Heart J* 1943 XXVI 631
- Evans W "The Relative Value of Certain Digitalis Preparations in Heart Failure with Auricular Fibrillation" *Brit Heart J* 1940 II 51
- Fahr G and LaDue J "A Preliminary Investigation of the Therapeutic Value of Lanatoside C (Digilamid C)" *Am Heart J* 1941 XXI 133
- Fothergill J M "Digitalis Its Mode of Action and Its Use An Enquiry Illustrating the Effect of Remedial Agents over Diseased Conditions of the Heart" *The Hastings Pri e Essay of the British Medical Association for 1870* Lindsay and Blackiston Philadelphia 1871
- Fraenkel A., and Doll H "Die intravenöse Strophanthintherapie und ihre Bedeutung für eine prognostische Beurteilung der chronischen Herzinsuffizienz" *Deutsch Arch f klin Med* 1923 CXLIII 65
- Fuchs L "De historia stirpium commentarii insignes maximis impensis et vigiliis elaborati adjectis earundem visis plus quam quingentis imaginibus" Basileae in officina I. I. gryniana 1442
- Gold H, Cattell McK et al "A Method for the Bioassay of Digitalis in Humans" *J Pharmacol & Exper Therap* 1942 LXXV 196
- "A Comparison of the Speed the Intensity and the Duration of Action of Four Digitalis Glycosides by Intravenous Injection in Man" *Proc Am Soc Exper Biol* 1943 II 80
- Gold H and DeGraff A C "Studies on Digitalis in Ambulatory Cardiac Patients II The Elimination of Digitalis in Man" *J Clin Investigation* 1939 VI 613
- Gold H, Kvit N T and Cattell McK "Studies on Purified Digitalis Glucosides I Potency and Dosage of Digitaline Natuelle by Oral Administration in Man" *J Pharmacol & Exper Therap* 1940 LXIX 177
- Hatcher W A "The Persistence of Action of the Digitalins" *Arch Int Med* 1917 X 68
- Jezer A and Schwartz S P "Auricular Fibrillation as an Early Toxic Digitalis Manifestation Further Observations on this Drug in Children with Congestive Heart Failure" *J Pediat* 1934 V 811
- LaDue J S., and Fahr G "The Effect of the Intravenous Administration of Lanatoside C Upon the Output Diastolic Volume and Mechanical Efficiency of the Failing Human Heart" *Am Heart J* 1943 XXV 344
- Luten D "The Clinical Use of Digitalis" Charles C Thomas Publisher Springfield, Ill 1936

- McGuire J and Richards C E "Fatal Digitalis Poisoning Occurring in a Normal Individual" *Am Heart J* 1936 XII 109
- Nativelle "Sur la digitale et sur la digitaline" *J de Chimie Médicale de Pharmacie et de Toxicologie* 1845 III Serie I 61
- Pardee H E B "Clinical Observations on the Use of Intravenous Digitalis Preparations" *J.A.M.A.* 1928 XCI 147
- Phang S H., and White P D "The Duration of Ventricular Systole as Measured by the Q T Interval of the Electrocardiogram with Especial Reference to Cardiac Enlargement with and without Congestive Failure" *Am Heart J* 1943 XXVI 108
- Pratt J H., and Morrison, H "The Activity of American Digitalis" *J.A.M.A.* 1919 LXXIII 1606
- Purkinje Joannes Ev *Beobachtungen und Versuche ur Physiologie der Sinne Sweetes Bandchen Neue Beitrage zur Kenntnis des Sehens in Subjectiver Hinsicht* Berlin 1825 G Reimer Opera Omnia, Tomus I Edited by Prof Dr Kamil Lhoták v Lhota for the Czech Medical Society (Spolek Českých Lékárů) Prague 1919
- Robinson, G C White P D Eggleston C and Hatcher R A "The Therapeutic Use of Digitalis with Especial Reference to Its Intravenous Injection" *J.A.M.A.* 1924 LXXXIII 504
- Schnitzer M A and Levine S A Presence of Digitalis in Body Fluids of Digitalized Patients" *Arch Int Med* 1937 LX 240
- Sokolow M., and Chamberlain, F L Clinical Experiences with the Oral Administration of Cediland and a Comparison of the Oral and Intravenous Preparations of Cediland with Digitalis Purpurea" *Am Heart J* 1942 XXIII 245
- Stewart, H J and Cohn A E "Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart" *J Clin Investigation* 1932 XI 897 917
- Stroud, W D Vanderveer J B and Leik D W "The Clinical Value of Digitaline Nativelle as Compared to Other Glucosides and Whole Leaf Preparations of Digitalis" *Tr Am Clin & Climatol A* 1935 LI 51
- Vaquez H and Leconte Les injections intra veineuses de strophantine dans le traitement d'insuffisance cardiaque *Bull et mem Soc med d hop d Paris* 1909 XXVII 667
- Weese H *Digitalis Thème* Leipzig 1936
- White P D and Mudd S G "Observations on the Effect of Various Factors on the Duration of the Electrical Systole of the Heart as Indicated by the Length of the Q T Interval of the Electrocardiogram" *J Clin Investigation* 1929 VII 387
- Withering W *An Account of the Foxglove and Some of Its Medical Uses With Practical Remarks on Dropsy and Other Diseases* M Swinney Birmingham 1785
- Wyckoff J and Goldring W "Intravenous Injection of Ouabain in Man" *Arch Int Med* 1927 XXXIX, 488
- Recent References (1944-1950)**
- Batterman R. C and Gutner L B "Increasing Congestive Heart Failure A Manifestation of Digitalis Toxicity" *Circulation* 1950 I 1052
- Batterman, R C and DeGraff A C "Comparative Study on the Use of the Purified Digitalis Glycosides Digoxin Digitoxin and Lanatoside C for the Management of Ambulatory Patients with Congestive Heart Failure" *Am Heart J* 1947 XXXIV 663
- Bine R Jr and Friedman M "The Serum Concentration of a Digitalis Glycoside and Its Rate of Disappearance in Patients After Parenteral Digitalization" *Am Heart J* 1949 XXXVII 623
- Cathcart E T and Blood D W "Effect of Digitalis on the Clotting of the Blood in Normal Subjects and in Patients with Congestive Heart Failure" *Circulation* 1950 I 1176
- Diefenbach W C and Meneely J K Jr "Digitoxin—Critical Review" *Yale J Biol & Med* 1949 XXI 421
- Geiling E M K Kelsey F E and McIntosh H J Biosynthesis of Radioactive Digitoxin Using Carbon 14 *Am Heart J* 1949 XXXVII 632
- Gilson J S and Schemm F R "The Use of Digitalis in Spite of the Presence of Ventricular Tachycardia" *Circulation* 1950 II 278
- Gold H Cattell McK Modell W Kwt N T Kramer M L and Zahm W

- Clinical Studies on Digitoxin (Digitaline Nativelle) *J Pharmacol & Exper Therap* 1944 XXXII 187
- Gripwall E Results of Treatment with Digitalis and Strophanthin "Nord med" 1949 XLII 1564
- Hilton J G A Polarographic Determination of Digitoxin *Science* 1949 CX 56
- Levine H Geller H M Sikand H S and Nahum L H Genesis of Electrocardiographic Pattern of Digitalis *Federation Proc Fed Am Soc of Exper Biol* 1951 X 82
- Master A M Digitoxin Intoxication *JAMA* 1948 CXXXVII 531
- Modell W Kwit N T Dayrit C Shane S J Zahm W Kramer M L and Gold H Studies on Purified Digitalis Glycosides VI Thevetin A Glycoside with Unusual Speed of Action in Man *J Pharmacol & Exper Therap* 1948 XCIV 44
- Stone J Auricular Tachycardia and Auriculo ventricular Dissociation Following 1<sup>st</sup> Mg of Digitoxin in One Dose *J Mt Sinai Hosp* 1948 XIV 9-4
- Sutton G C Studies on Blood Coagulation and the Effect of Digitalis *Circulation* 1950 II 271
- Vos B J Jr and Braun H A The Potency of Strophanthin USP XII "Federation Proc Fed Am Soc Exper Biol" 1945 IV 139

### Diuretics

- Batterman R C DeGraff A E and Rose O A Treatment of Congestive Heart Failure with an Orally Administered Mercurial Diuretic *Am Heart J* 1941 XXI 98
- Blum L L'action diurétique du bismuth: mécanisme de cette action *Compt rend Soc d biol d Paris* 1923 LXXXVIII 461
- Blumgart H L Gilligan D R Levy R C Brown M G and Volk M C Action of Diuretic Drugs I Action of Diuretics in Normal Persons *Arch Int Med* 1934 LIV 40
- Crawford J H and McIntosh J F "The Use of Urea as a Diuretic in Advanced Heart Failure" *Arch Int Med* 1925 XXXVI 530
- DeGraff A C Batterman R C and Lehman R A "Influence of Theophylline on Absorption of Mercupurin and Salyrgan from Site of Intramuscular Injection" *J Pharmacol & Exper Therap* 1938 LXII 26
- DeGraff A C Cowett M and Batterman R C Rectal Irritation Following the Use of Mercurial Diuretics in Suppository Form *JAMA* 1939 CXIII 214
- Evans W and Faxon T A Comparison of the Mercurial Diuretics Used in Heart Failure *Brit Heart J* 1941 III 112
- Fox R Gold H and Leon J Hypersensitiveness to a Mercurial Diuretic *JAMA* 1942 CXIX 1497
- Gamble J L Blackfan K D and Hamilton H A Study of the Diuretic Action of Acid Producing Salts *J Clin Investigation* 1925 I 359
- Goodman J I et al Mercurial and Xanthine Diuretics in Chronic Congestive Heart Failure Comparative Survey" *Arch Int Med* 1942 LXX 975
- Herrmann G Schwab E H Stone C T and Marr W L On the Advantage of Alternating Vegetable and Metallic Diuretics in Treatment of Edema of Congestive Heart Failure" *J Lab & Clin Med* 1933 XVIII 902
- Jendrassik H "Kalomel als Diuretikum" *Deut ch Arch f klin Med* 1886 XXXVIII 499
- Keith N M Barrier C W and Whelan M The Diuretic Action of Ammonium Chloride and Novasurol" *JAMA* 1925 LXXXV 799
- Keith N M and Binger M W Diuretic Action of Potassium Salts *JAMA* 1915 CV 1584
- Marvin H M "The Value of the Xanthine Diuretics in Congestive Heart Failure" *JAMA* 1926 LXXVII 2043
- Maxwell F S Scott J W and Harvey J "A Study of the Effect of Mercurial Diuretics on Kidney Disease" *JAMA* 1933 CI 2074
- Osler W "Calomel as a Diuretic" *At News Philadelphia* 1887 L, 268 1888 LIII 593
- Saxl P and Heilig R "Ueber die diuretische Wirkung von Novasurol und anderen Quecksilberinjektionen" *Wien klin Wchnschr* 1920 XXXIII 943 (Introduction of injections of mercury salts for diuresis)

- Walsh B J and Sprague H B "The Treatment of Congestive Failure in Children with Active Rheumatic Fever" *J IMA* 1941 CXVI 560
- Wiseman J R "The Prolonged Use of Salyrgan as a Diuretic Report of 270 Injections in Five Years in One Case" *JAMA* 1932 XCIX 114

#### Recent References (1944-1950)

- Batterman R C DeGraff A C and Shorr H M Further Observations on the Use of Mercupurin Administered Orally *Am Heart J* 1946 XXXI 431
- Batterman R C Unterman E and DeGraff A C "The Subcutaneous Use of Thimerin A New Mercurial Diuretic for Treatment of Congestive Heart Failure" *JAMA* 1949 CXL 1268
- Enselberg C D and Simmons H G Clinical Experience with Thimerin Observations on its Use in 205 Patients *Am J M Sc* 1950 CCXIX 139
- Kaufman R E Immediate Fatalities after Intravenous Mercurial Diuretics *Ann Int Med* 1948 XXVIII 1040
- Krehbiel E and Stewart H J "Self administration of a Mercurial Diuretic Experience of Patients with Mercaptomerin (Thimerin) Sodium" *JAMA* 1951 CXLVI 250
- Modell W Gold H and Clarke D A "Quantitative Observations on Mercuhydrin and Mercupurin" *J Pharmacol & Exper Therap* 1945 LXXXIV 284
- Ross P H and Grau E Massive Response to a Mercurial Diuretic in a Case of Congestive Heart Failure" *Ann Int Med* 1950 XXIX 335
- Stanley T E "Analysis of 27 Reported Fatalities Immediately Following Injection of Mercurial Diuretic" *Virginia M Monthly* 1949 LXXVI 416

#### Other Drugs in Congestive Failure

- Arnold H L Middleton W S and Chen K J The Action of Thevetin, a Cardiac Glucosid and Its Clinical Application *Am J M Sc* 1935 CLXXXIX 193
- Barach A L The Therapeutic Use of Oxygen in Heart Disease *Ann Int Med* 1931 V 428
- Use of Helium as a New Therapeutic Gas *Proc Soc Exper Biol & Med* 1934 XXXII 462
- Boothby W M Mayo C W and Lovelace W R II One Hundred Per Cent Oxygen" *JAMA* 1939 CXIII 477
- Marvin H M and White P D Clinical Studies of Drugs of the Digitalis Series III Apocynum and Convallaria *JAMA* 1921 LXXVII 1865
- Richards D W Jr and Barach A L "Prolonged Residence in High Oxygen Atmospheres Effects on Normal Individuals and on Patients with Chronic Cardiac and Pulmonary Insufficiency" *Quart J Med* 1934 III 437
- Stroud W H and Twaddle P H Observations upon the Effect of Coramine in Certain Cardiac States *Ann Int Med* 1940 XIV 361
- White P D Balboni G M and Viko L E Clinical Observations on the Digitalis like Action of Squill *JAMA* 1920 LXXV 971

#### Recent References (1944-1950)

- Anderson G M and Hull E The Effect of Dicumarol Upon the Mortality and Incidence of Thromboembolic Complications in Congestive Heart Failure *Am Heart J* 1950 XXXIX 697
- Berger E Y Irwin L Rosenberg E and Jackenthal R The Effect of a Cation Exchange Resin on Electrolyte Balance and Its Use in Edematous States *J Clin Investigation* 1949 XXVIII 770
- Currens J H Counihan T and Rourke M Observations on the Administration of Ammonium Cation Exchange Resin to Patients with Cardiac Edema *J Clin Investigation* 1950 XXIX 807
- Dock W and Frank N R Cation Exchangers Their Use and Hazards in Managing Edema *Am Heart J* 1950 XL 634
- Howarth S McMichael J and Sharpey Schafer E P The Circulatory Action of Theophylline Ethylene Diamine *Clin Sc* 1947 VI 15

- Levy H and Boas E P Vitamin E in Heart Disease *Ann Int Med* 1948 XXVIII, 1117
- McChesney E W Dock W and Tainter M L Ion Exchange Resins in Edema *Medicine* 1951 XXX 183
- Modell W et al Studies on Purified Digitalis Glycosides VI Thevetin A Glycoside with Unusual Speed of Action in Man *J Pharmacol & Exper Therap* 1948 XCIV 44

### Diet Fluids and Salt in Heart Failure

- Barker M H Edema as Influenced by a Low Ratio of Sodium to Potassium Intake *JAMA* 1932 XCVIII 2193
- Ellis L H "The Relative Importance of Salt and Fluids in the Management of Congestive Heart Failure" *Tr New England Heart A* 1942 p 3
- Karell P De la cure de l'asthme *Arch gen d med* 1866 II 513
- Proger S Ginsburg E and Magendantz H "The Effects of the Ingestion of Excessive Amounts of Sodium Chloride and Water of Patients with Heart Disease" *Am Heart J* 1942 XXIII 555
- Schemm F R High Fluid Intake in Management of Edema Especially Cardiac Edema I Details and Basis of Régime *Ann Int Med* 1942 XVII 952 "II Clinical Observations and Data" *Ibid* 1944 XXI 937
- Schroeder H A Studies on Congestive Heart Failure I The Importance of Restriction of Salt as Compared to Water *Am Heart J* 1941 XXII 141
- Strauss H *The Diet Treatment of Internal Diseases* S Karger Berlin 1908
- Widal and Lemerre Pathogenie de certains oedèmes brightiques action du chlorure de sodium ingere *Bull et mém Soc med d hop de Paris* 1903 XX 678

### Recent References (1944-1950)

- Bryant J M Job V Phillips G L and Blecha E M Estimation of Urinary Sodium A Simple Test for Patients on Low Sodium Diet *JAMA* 1949 CXL 670
- Cole S L "Tap Water Sodium in the Low Salt Diet" *JAMA* 1949 CXL 19
- Dock W Sodium Depletion and Therapeutic Procedure The Value of Ion Exchange Resins in Withdrawing Sodium from the Body" *Tr A Am Physicians* 1946 LIV, 82
- Iseri L T Boyle A J Rosow W A Griffin R and Engstrom F Metabolic Studies During Treatment of Severe Congestive Heart Failure with 50 mgm Sodium Diet *J Clin Investigation* 1950 XXIX 825
- Jaffe H L Master A M and Dorrance W "The Salt Depletion Syndrome Following Mercurial Diuresis in Elderly Persons" *Am J Med Sc* 1950 CCXX 60
- Kempner W "Treatment of Kidney Disease and Hypertensive Vascular Disease with Rice Diet" *North Carolina M J* 1944 V 125 and 273 1945 VI 61 and 117
- Lyons R H Jacobson S D and Avery M L Change in Plasma Volume and Body Weight in Normal Subjects After Low Salt Diet Ammonium Chloride and Mercuripurin" *Am J Med Sc* 1946 CCXI 460
- Schemm F R "Certain Clinical Aspects of the Application of Water Balance Principles to Heart and Kidney Disease" *Ann Int Med* 1949 XXV 92
- Schroeder H A "Renal Insufficiency Caused by Overhydration or Depression of Sodium Chloride The Low Salt Syndrome" *J Clin Investigation* 1949 XXVIII 809
- Talbott J H "Use of Lithium Salts as a Substitute for Sodium Chloride" *Arch Int Med* 1950 LXXXV 1
- Wheeler E O Bridges W C and White P D Diet Low in Salt (Sodium) in Congestive Heart Failure *JAMA* 1947 CXXXIII 16

### Other Treatment of Heart Failure

- Blumgart H L "Analysis of the Results of Total Thyroidectomy in the Treatment of Congestive Heart Failure in 27 Cases" *Personal communication* 1936 194
- Blumgart H L Levine B A and Berlin D D Congestive Heart Failure and Angina Pectoris Therapeutic Effect of Thyroidectomy on Patients Without Clinical or Pathologic Evidence of Thyroid Toxicity" *Arch Int Med* 1933 LI 866

- Brauer L. Ueber chronische adhesive Mediastino Perikarditis und deren Behandlung " *Munch med Wchnschr* 190 XLIX 1072 1732
- Southey R. "Traitement de l'anasarque général par un drainage Capillaire " *Compte rendu de la 6 Session Association Française pour l'Avancement de Sciences* Le Havre 1877 857

*Recent References (1944-1950)*

- Blumgart H L Freedberg A M and Buka R "Treatment of Euthyroid Cardiac Patients by Producing Myxedema with Radioactive Iodine *Proc Soc Exper Biol & Med* 1948 LXVII 190
- Fiese M J and Thayer J M "Value of Southey Leech Tubes in Rapid Relief of Massive Edema *Arch Int Med* 1950 LXXXV 132



# DISORDERS OF VASCULAR FUNCTION INCLUDING GENERAL VASCULAR FAILURE (SHOCK) AND RAYNAUD'S DISEASE

---

An essential factor in the maintenance of the circulation of the blood is the proper functioning of the arterioles and venules. Disorders of vascular function comprise an important example of the failure of adaptation of the human organism and can have important consequences. They are of two main types: (1) general vascular disorders which are likely to be serious and (2) local involvement of the peripheral circulation as in Raynaud's disease with little or no influence on the heart itself or on the health as a whole although at times causing great discomfort. These types together constitute a section of the field of normal and abnormal cardiovascular physiology which is becoming better understood and more clearly defined but which is still in need of further exploration. As stated in the last edition of this book, neither exact knowledge of the mechanism of these vascular disorders nor their therapy has as yet reached a stage comparable to that of the understanding of disorders of function of the heart itself. Although it is certain that knowledge of vascular disorders will gain many additions in the future as it had indeed already done during the last generation, it is not likely that this chapter will ever become the most important part of a survey of cardiovascular disease as a whole as has sometimes been intimated. The heart perforce remains the most vital part of the circulatory apparatus.

Functional vascular disorders consist of an abnormal degree of distribution of vasoconstriction and vasodilatation and of an abnormal permeability of the walls of the smallest blood vessels. There may be an abnormal degree of vasoconstriction in one part of the body coexistent with abnormal vasodilatation in another part. Just how much the two opposite conditions of vasoconstriction and vasodilatation may be due to local vascular irritability, how much to the direct effect of toxins on the vessel walls and how much to nervous stimulation central and peripheral still remains in many cases difficult or impossible to say.

## GENERAL OR EXTENSIVE DISORDERS OF VASCULAR FUNCTION

**Vasoconstriction** Experimentally general vasoconstriction can be produced by the action of certain drugs especially epinephrine (adrenaline) and Pituitrin by direct electric stimulation of the sympathetic nerves and by indirect sympathetic stimulation by fear excitement cold and the toxic condition that causes a shaking chill

Clinically there is reason to believe that general vasoconstriction by increasing the resistance to the circulation of blood is responsible for *essential hypertension* or *hyperpiesia*. If such a mechanism exists as seems likely it yet remains to be discovered whether the vasoconstriction is always due directly to some renal metabolic or extraneous toxin in the blood stream to sympathetic nerve effect from central stimulation or to local irritability of unknown cause widespread throughout the vascular tree. A crystalline pressor substance called angiotonin or hypertensin has been isolated in recent years from the reaction of a renal extract (renin) and renin activator (Houssay, Fasciolo and Taquini 1938 Page et al 1940). Latterly tests of vasomotor lability have been introduced to determine the degree to which generalized vasoconstriction can be influenced and thus judged as to possible amenability to sedative or dilatation therapy or to sympathectomy and also perhaps in picking out potential hypertensive cases. These have been called the cold pressor test and the sedation test. They consist of noting the effect on the blood pressure of immersing one hand for one minute in ice cold water (normally except in very sensitive persons the blood pressure should not rise over 15 mm mercury systolic—Hines and Brown 1933) and of recording the low levels to which systolic and diastolic blood pressures drop hourly for 12 hours after the administration of 0.2 gm (3 gr) of Sodium Amytal by mouth each time at 7, 8 and 9 o'clock in the evening (see Chapter 19).

**Vasodilatation** Experimentally general vasodilatation can be produced by various poisons and by sympathetic nerve depression. Certain sensitive individuals are more prone to such vasomotor disturbances than are others and the same person will react differently at different times. Now and then an otherwise healthy young person will faint under the stress of some simple procedure such as the taking of the blood pressure or standing at attention. Also the simple pooling of blood in varicose veins may cause dizziness and other symptoms. Extensive vasodilatation may be preceded by a short interval of vasoconstriction.

**Vascular shock or failure** General peripheral circulatory failure is a serious state characterized by progressive loss of circulating blood volume due to generalized increase in capillary permeability. Two explanations have been advanced to account for this widespread change in capillary permeability: first that it results through the action of some toxic factor absorbed from the area of injury and second that the increase in capillary permeability is caused by the tissue anoxia which results from reduced circulation. (Freeman 1942).



**Drugs** The administration of caffeine in large dosage by mouth subcutaneously or intravenously (10 to 15 gr of caffeine sodiobenzoate) at intervals of three or four hours is only palliative though it may help Epinephrine (adrenaline) hydrochloride injected intravenously or intramuscularly in the dose of 0.5 to 1 cc of a 1:1000 solution and Pituitrin (or the derivative Pitressin containing the active pressor principle with little or none of the oxytocic principle which causes uterine contractions and is used in obstetrics) injected intramuscularly or subcutaneously in the dose of 0.5 to 1 cc (equivalent to 0.1 to 0.2 gr of the posterior lobe of the pituitary gland) have also been recommended for use in shock but their action is uncertain and likely to be followed by unfavorable after-effects such as increase in the vasodilatation after the transient vasoconstriction or a primary vasodilatation itself. The difficulty with epinephrine and Pituitrin is that they act on the arterioles whereas the fault lies in the lack of tone in capillaries and venules. Cortical extract has been tried with apparent benefit as a prophylactic against experimental shock in animals and surgical shock in man (Helfrich Cassels and Cole 1942) but its beneficial effect has not been confirmed. Drugs such as digitalis and strophanthin directed at the heart itself have proved of no avail and may do harm. The heart in such cases is struggling with an inadequate supply of blood and needs no direct stimulation for itself *it should not be slowed*.

Of late years it has been agreed that *circulatory failure caused by acute infections* should be separated as to findings and treatment from that of hemorrhagic or traumatic shock. Ebert and Stead (1941) found in cases of lobar pneumonia with bacteremia and of streptococcal and staphylococcal septicemia with circulatory failure characterized by a decrease in peripheral blood flow and a fall in arterial pressure that measurements of the hematocrit level serum protein concentration and plasma volume showed no significant hemoconcentration or diminished blood volume that the venous pressure was normal and that elevating the foot of the bed and transfusing with whole blood did not produce any improvement in the circulation. They concluded that the entire cardiovascular system was depressed or damaged by the infection with simultaneous injury to the heart and loss of venous tone and that therapy must be directed toward overcoming the infection rather than attempting to treat the circulatory failure per se. It may be that shock associated with the acute infections differs from traumatic shock in large part only in the persistence of the exciting factor and not so much in a cardiac factor—which illustrates the need for more light on all the types and mechanisms of what we now call circulatory failure.

*The shock syndrome produced by acute myocardial infarction or acute congestive heart failure* may need to be differentiated from the circulatory failure secondary to hemorrhage accident operation or infection. When along with signs of diminished peripheral blood flow there is congestion of the pulmonary or of the systemic venous bed the clinical picture of shock is often to be ascribed rather to the heart failure than to an inadequate venous

return of blood to the heart resulting from decrease in blood volume or pooling of blood in the peripheral circulation (Stead and Ebert 1942) There are however cases in which doubtless both factors are responsible primarily acute coronary occlusion or acute congestive heart failure and secondarily vascular failure

### LOCAL DISORDERS OF VASCULAR FUNCTION

**Vasoconstriction:** Experimentally and physiologically vasoconstriction of a single artery or of a group of arteries can be easily induced by direct irritation by the application of cold and toxic agents to the vessel itself or to the skin over the superficial arteries involved or by the stimulation of the sympathetic nerves controlling the vessels

**Vascular crises** Clinically there are a few abnormal states which are undoubtedly dependent on local vasoconstriction One of these is the so-called vascular crisis or spasm involving cerebral retinal coronary or other arteries supplying such vital tissue that important symptoms are quickly produced if the blood supply to this tissue is cut off (Pal, 1905) Transient dizziness syncope paralysis tinnitus and visual disturbances lasting a few seconds to a few minutes have been commonly reported and thought to be due to local vasoconstriction of somewhat abnormal and irritable vessels such vascular crises occur for the most part in persons over fifty years of age who have hypertension It is often difficult to rule out in such cases slight lesions—hemorrhagic embolic or thrombotic in nature—but it is quite certain that vascular crises do occur Retinal arterial spasm has actually been observed and recently it has been proved experimentally that the cerebral arteries are under sympathetic nerve control Although intermittent claudication (pain in the calves on walking) may in some instances be due to vascular crises it is more likely that permanent arterial narrowing is responsible there the circulation being adequate when the muscles are at rest nevertheless the benefit that sometimes results in these cases from lumbar sympathectomy or procaine injection indicates that there may well be a considerable superimposed vasoconstriction (Freeman and Montgomery 1942) It is possible that vascular crises (coronary spasms) are at times a factor in the production of angina pectoris When there is a general vasoconstricting storm producing paroxysmal hypertension with or without angina pectoris the condition has been called *Nothnagel's syndrome* (Nothnagel 1867) This should not include paroxysmal hypertension due to a pheochromocytoma Also in recent years Pickering (1948) has shown that much of the so called cerebral vascular spasms constituting a major part of hypertensive encephalopathy is in reality a succession of cerebral vascular accidents (hemorrhage or thrombosis) leaving minute scars of infarction behind them

**Raynaud's disease** is a spasmodic vasoconstriction of unknown cause affecting the extremities usually both hands often preponderantly either right or left and rarely the feet It causes blanching of the skin a decrease in pulse and symptoms of pain and numbness The syndrome recurs periodically at

longer or shorter intervals (days weeks or months) lasts a few minutes to a few hours at a time and is induced especially by exposure to cold and to nervous excitement when severe trophic disturbances appear and even gangrene may result (Raynaud 1862) In the late stages the arteries themselves become structurally diseased with thickened walls and narrowed lumina and in some cases of Raynaud's disease similar changes have been found in the small vessels of the lungs with extensive pulmonary fibrosis (Linenthal 1942)

Raynaud M *De l'asphyxie locale et de la gangrene symetrique des extremités*  
Thesis Rignoux Paris 1862

The following passages from this pioneer work are of interest (Translation by myself)

#### From the Preface

'To describe a new disease and above all to give a new name to a group of symptoms which have been long observed and described is a matter certainly less difficult than to associate several apparently different affections under a common law which controls them

Moreover in spite of the title which I have given to this thesis I wish to state at the outset that I have no aspiration to the empty and dangerous honor of pathological innovation Facts are always but facts and there is advantage only in grouping them in orderly arrangement

#### From Chapter I page 17

I propose to demonstrate that there exists a variety of dry gangrene affecting the extremities which cannot be explained by vascular obliteration a variety characterized especially by a remarkable tendency to symmetry to such a degree that it always affects similar parts the arms or legs or all four extremities at one time and even in certain cases the nose and ears also I shall try to prove that this kind of gangrene has its origin in a defective innervation of the capillary vessels which will remain for me to describe

As one can see this is a very restricted corner of the general subject of gangrene which I am now undertaking to discuss

#### From Chapter III page 109

II In order to arrange more satisfactorily the symptomatology and to avoid confusing very different conditions because of their serious nature I shall describe separately local syncope and asphyxia on the one hand and symmetrical gangrene of the extremities on the other

In its simplest form local syncope is a condition perfectly compatible with good health Individuals who have this trouble and who are usually women notice that under the slightest influence sometimes without any appreciable cause one or more of their fingers grow suddenly pale and cold In many cases it is always the same finger that is first affected the others become deadened successively always in the same order This phenomenon is known under the name of *doigt mort* (dead finger) The attack is painless and lasts from a few minutes to several hours The provoking cause is often the feeling of cold what happens ordinarily only under the influence of the most severe cold occurs in the subjects of whom we are now speaking as the result of the slightest drop in temperature sometimes

a simple emotional disturbance is sufficient to produce this effect. It appears that the same cause which acts on the capillaries of the face and produces a blush can under the circumstances exert its action especially on the capillaries of the extremities.

The skin of the affected parts assumes a dull white or at times a sallow shade; it appears completely exsanguinated. The cutaneous sensibility diminishes and then disappears; the fingers become like strangers to their owners. Their temperature drops notably. The attack is followed by a reaction which is often very painful and which gives rise to a sensation quite like that of a numb cold in the fingers. In cases more pronounced especially in those with pre-dominant asphyxia the discoloration of the extremities is replaced by a cyanotic tint of various shades.

#### Page 129 *Ætiology VIII*      A Predisposing causes

*Sex* This influence is very pronounced in favour of the female sex. Of my 75 cases 20 were in women and only 5 in men.

*Age* The influence of age is no less important and to such a degree that one would be almost tempted to reserve for the condition the name juvenile gangrene. In the great majority of cases the malady appears between the ages of 18 and 30 years the average of 25 years constituting a time of marked predisposition.

*Temperament constitution previous illnesses* Although all temperaments are subject to this malady individuals of lymphatic and nervous nature are particularly prone.

Evidence has been published (Lewis 1929) to indicate that for some unknown reason the palmar arteries are unusually irritable in themselves in Raynaud's disease but other evidence still supports Raynaud's original contention that there is also an important nervous element in the pathogenesis of this disease (White J C 1932). Sympathetic ganglionectomy has been carried out in the treatment of Raynaud's disease with definite relief (Adson and Brown 1929 Mayo and Adson 1932). It has been reported (Agate 1949) that a high percentage of workers who polish metal castings with rotary tools show intermittent pallor of their hands.

A form of diffuse scleroderma has been found by Lewis and Landis (1931) to be due to a vascular defect similar to that noted in some cases of Raynaud's disease.

*Vasodilatation* Vasodilatation is easily induced locally by the application of heat and by traumatic skin lesions. Exercise of a muscle increases very much the blood flow through it dilatation of the local arteries and arterioles bringing this about. Sympathectomy temporary paralysis of the sympathetic nerve connections by local anesthetic (as with novocaine) and permanent destruction of the sympathetic fibers by the injection of alcohol cause vasodilatation of the blood vessels in the part of the body affected and these measures have been employed in the treatment of trophic disorders and of pain which may result from abnormal vasoconstriction.

*Blushing* is a common phenomenon due to local effects on the peripheral arterioles especially in the face from nervous excitement.

Chronic dilatation of the blood vessels in certain parts of the body *telang ectasis* (τελος end α/ρειος vessel and εκτασις development) especially in the face may follow alcoholism or constant or repeated exposure to the atmosphere of raw climates it is frequently also a congenital defect

There are two other local pathologic skin conditions dependent mainly on abnormal vasodilatation These are the common *chilblain*—an acute painful or itching reddened area of skin usually of hand or foot—due to prolonged exposure to cold and wet especially in sensitive individuals and the rare *erythromelalgia* (ριθρος red μελο limb and αλγος pain) of unknown cause consisting of a paroxysmal abnormal local vasodilatation of the extremities with redness throbbing and pain not usually leading to any trophic disturbance (Weir Mitchell 1878)

Finally the trauma or toxin that causes local or general vasodilatation may set free from the tissues a histamine like substance which acts on the walls of the smaller blood vessels allowing the exudation of fluid into the perivascular tissues this is most readily seen under the skin in the form of wheals *urticaria* (from the Latin *urtica* nettle) (Lewis and Grant 1924)

## BIBLIOGRAPHY

SEE ALSO REFERENCES ON CAPILLARY CIRCULATION AND BLOOD FLOW IN CHAPTER 6  
VASCULAR DISEASE CHAPTER 28 AND DISORDERS OF FUNCTION CHAPTER 29

- Adson A W and Brown G E Raynaud's Disease of the Upper Extremities Successful Treatment by Resection of the Sympathetic Cervicothoracic and Second Thoracic Ganglions and the Intervening Trunk *JAMA* 1929 XCII 444
- Allen E V The Peripheral Arteries in Raynaud's Disease An Arteriographic Study of Living Subjects *Proc Staff Meet Mayo Clin* 1937 XII 187
- Bialock A Peripheral Circulatory Failure *Am Heart J* 1942 XXIII 147
- Cannon W B *Traumatic Shock* Appleton Century-Crofts Inc New York 1923
- Chapman E M and Asmussen E On the Occurrence of Dyspnea Dizziness and Precordial Distress Occasioned by the Pooling of Blood in Varicose Veins *J Clin Investigation* 1942 XXI 393
- Dale H H The Nature and Cause of Wound Shock *Harvey Lectures* 1919-20 XV 6
- Ebert R V and Stead E A Jr Circulatory Failure in Acute Infections *J Clin Investigation* 1941 XX 671
- Freeman N E Shock *Mod Concepts Cardiovas Dis* 1942 XI No 9
- Freeman N E and Montgomery H Lumbar Sympathectomy in the Treatment of Intermittent Claudication *Am Heart J* 1942 XXIII 224
- Helfrich L G Gassels W H and Cole W H Cortical Extract in Treatment of Shock *Am J Surg* 1947 LV 410
- Henderson Y The Venopressor Mechanism *Science* 1941 XCV 539
- Hines E A Jr and Brown G E A Standard Test for Measuring the Variability of Blood Pressure Its Significance as an Index of the Prehypertensive State *Ann Int Med* 1933 VII 209
- Houssay B A Fasolo J C and Taquini A C Mecanismo de la hipertension arterial de origen renal *Rev Argentina d Cardiol* 1938 V 291
- Krogh A *The Anatomy and Physiology of Capillaries* Yale University Press New Haven 1922



Lewis T Experiments Relating to the Peripheral Mechanism Involved in Spasmodic Arrest of the Circulation in the Fingers a Variety of Raynaud's Disease" *Heart* 1919 XV 7

*Vascular Disorders of the Limbs* Macmillan Co New York 1936

Lewis T and Grant R T Vascular Reactions of the Skin to Injury Part II The Liberation of a Histamine Like Substance in Injured Skin The Underlying Cause of Factitious Urticaria and of Wheals Produced by Burning And Observations Upon the Nervous Control of Certain Skin Reactions *Heart* 1924 XI 209

Lewis T and Landis E M Further Observations upon a Variety of Raynaud's Disease with Special Reference to Arteriolar Defects and to Scleroderma *Heart* 1931 XV 329

Linenthal H Observations Concerning Pulmonary Fibrosis in Raynaud's Disease *New England J Med* 1942 CCXXVII 433

Mayo W J and Adson A W Raynaud's Disease Thrombo Angiitis Obliterans and Scleroderma Selection of Cases for and Results of Sympathetic Ganglionectomy and Trunk Resection *Ann Surg* 1932 XCVI 771

Mitchell W On a Rare Vaso Motor Neurosis of the Extremities and on the Maladies with Which It May Be Confounded *Am J M Sc* 1878 LXXVI 1

Nothnagel H Zur Lehre von den vasomotorischen Neurosen *Deutsch Arch f klin Med* 1867 II 173

Page I H and Helmer O M A Crystalline Pressor Substance (Angiotonin) Resulting from the Reaction between Renin and Renin activator *J Exper Med* 1940 LXXI 29

Pal J *Gefassskrisen* S Hirzel Leipzig 1905

*Die Tonuskrankheiten des Herzens und der Gefasse Ihre Biologie und Therapie* Julius Springer Vienna 1934

Porter W T Traumatic Shock *Harvey Lectures* 1917-19 XIII-XIV 21

Raynaud A G N *De l'asphyxie locale et de la gangrene symétrique des extrémités* Thesis Rignoux Paris 1862

Sheehan H L Subendocardial Hemorrhages in Shock *Lancet* 1940 I 831

Smith L A and Allen E V "Erythralgia (Erythromelalgia) of the Extremities A Syndrome Characterized by Redness Heat and Pain *Am Heart J* 1938 XVI 175

Smithwick R H The Rationale and Technic of Sympathectomy for the Relief of Vascular Spasm of the Extremities *New England J Med* 1940 CCXXII 699

Stead E A Jr and Ebert R V Shock Syndrome Produced by Failure of Heart *Arch Int Med* 1947 LXIX 369

White J C "Raynaud's Disease Studies on Post Operative Cases Bearing on the Etiology of the Disease and the Efficiency of Sympathetic Ganglionectomy *New England J Med* 1932 CCVI 1198

#### Recent References (1944-1950)

Agate J N "Outbreak of Cases of Raynaud's Phenomenon of Occupational Origin *Brit J Indust Med* 1949 VI 144

Aub J C et al Bacteria and the Toxic Factor in Shock *War Med* 1944 V 71

Burnett C H Bland E F and Beecher H K Electrocardiograms in Traumatic Shock in Man" *J Clin Investigation* 1945 XXIV 687

Ciliberti H J and Dickler D J Intra arterial Transfusions in Hemorrhagic Emergencies Complete Recovery Following Massive Pulmonary Artery Hemorrhage *JAMA* 1950 CXLIV 382

Felder D A Simeone F A Linton H R and Welch C E Evaluation of Sympathetic Neurectomy in Raynaud's Disease Based on Follow up Study of 40 Patients *Surgery* 1949 XXVI 1014

Gardner W J and Hale D E "Arterial Bloodletting During Operation as Aid in Hemostasis" *Am J Surg* 1950 LXXXIX 635

Holden W H Cole J W and Portmann A F Myocardial Intolerance to Excessive Blood Transfusion" *Surg Gynec & Obst* 1950 XC 455

Kleckner M S Jr Allen E V and Wakim K G The Use of Glyceryl Trinitrate (Nitroglycerin) Ointment in the Treatment of Raynaud's Disease and Raynaud's Phenomenon." *Proc Staff Meet Mayo Clinic* 1950 XXV 657

- Nathanson, I T et al "The Toxic Factors in Experimental Traumatic Shock I Physiologic Effects of Muscle Ligation in the Dog" *J Clin Investigation* 1945 XXIV 829
- Page I H "On Certain Aspects of the Nature and Treatment of Oligemic Shock" *Am Heart J* 1949 XXXVIII 161
- Pickering G W "Transient Cerebral Paralysis in Hypertension and in Cerebral Embolism With Special Reference to the Pathogenesis of Chronic Hypertensive Encephalopathy" *JAMA* 1948 CXXXVII 4-3
- Prinzmetal M Freed S C and Kruger II E "Pathogenesis and Treatment of Shock Resulting from Crushing of Muscle" *War Med* 1944 V 74
- Robertson E L Trinchler I H and Dennis E W "Intra Arterial Transfusion Experimental and Clinical Considerations" *Surg Gynec & Obst* 1948 LXXXVII 695
- Stead E A Jr Brannon E S Merrill A J and Warren J V "Concentrated Human Albumin in Treatment of Shock" *Arch Int Med* 1946 LXXVII 564
- Van Slyke D D "The Effects of Shock on the Kidney" *Ann Int Med* 1948 XXVIII 701
- Wiggers C J "Myocardial Depression in Shock" *Am Heart J* 1947 XXVIII 633
- Wiggers H C Ingraham R C Roemhild F and Goldberg H "Vasoconstriction and the Development of Irreversible Hemorrhagic Shock" *Am J Physiol* 1948 CLIII 511

### PREMATURE BEATS (EXTRASYSTOLES) PAROXYSMAL TACHYCARDIA

Not much revision has been found necessary in the case of the last three chapters of the book but they have been carefully reviewed to bring them fully up to date

---

The commonest and simplest abnormalities of cardiac rhythm are premature beats (or extrasystoles) and paroxysmal tachycardia. Related in mechanism and often occurring in the same patient they are of but little clinical significance. Their frequency and likelihood of overemphasis render them however a subject of some importance.

#### PREMATURE BEATS

Premature contractions of the heart or extrasystoles as they are sometimes called are due to abnormal or re entry stimuli in various parts of the heart atria ventricles atrioventricular bundle and even the nodes themselves. A perfectly satisfactory term is difficult to find. Premature beat or premature contraction seems most suitable because the chief feature of this abnormality of mechanism is its prematurity. On rare occasions, however when it happens that the normal (sinoatrial nodal) pacemaker is depressed and the normal beat delayed there may be an abnormal or ectopic beat which is not premature. The term extrasystole in common use is less suitable in that the premature beat is only rarely a true extra or additional systole it merely comes early and replaces the normal systole. If extra is taken to mean 'ectopic' that is, arising from an abnormal point it is more suitably applied but it is also possible to have a premature beat which arises in or very close to the normal pacemaker.

**Incidence** The premature beat is almost universal. Probably only a very rare individual escapes having premature beats at some time of his life although they often pass unnoticed. It is without doubt the commonest of all cardiac abnormalities in fact it is so frequent among otherwise normal individuals that it hardly deserves the name of abnormality.

**Mechanism (abnormal physiology)** A wave of excitation and contraction may arise abnormally in the heart spreading from a point outside the limits of the normal pacemaker (sinoatrial node) or rarely from within the normal pacemaker itself (and then called *nomotopic*). The stimulus must occur at a time when the muscle will respond that is when it is not still in the refractory (unresponsive) phase due to the existence of a state of contraction or recovery. It is possible that the premature beat may be the result of the re-entry of the previous normal (or abnormal) excitation wave by way of an area of muscle refractory to the direct spread of the wave but recovering sufficiently to allow response a little later to the same excitation wave reaching it slowly in a round-about course.

(a) *Atrial premature beat* An abnormal wave starting in the atrial muscle spreads in all directions: it not only descends to the atrioventricular junctional tissue thus giving rise to a ventricular response but it also ascends to the sinoatrial node thus discharging a normal impulse already in the process of development, and so interrupting the dominant rhythm. The atrial premature beat whose atrial component in the electrocardiogram (*P* wave) is usually inverted is followed by a pause which is equivalent to the time interval needed for its impulse to reach the sinoatrial node plus the usual time interval between two normal sinoatrial contractions. This pause plus the time interval between the normal beat just preceding the atrial premature beat and the atrial premature beat itself gives an interval less than that covered by two normal beats; hence this pause is not compensatory: the spacing of the groups of beats in electrocardiogram and arteriogram is interfered with and the dominant rhythm is disturbed (Figure 154 page 868).

Usually the ventricles respond to an atrial premature beat but often they do so in an abnormal way that is there is a state of intraventricular block or defective conduction in the bundle branches: such block is doubtless due to relative degrees of refractoriness (or slowness of recovery from the previous contraction) in various parts of the conducting system. The earlier the atrial premature beat the more likely is the ventricular response to be abnormal that is to show intraventricular block. Such abnormal response has not been found to be of any clinical significance as it is a more or less normal transient functional condition. Rarely the ventricles may fail to respond at all to atrial premature beats: this lack of response is not remarkable if the abnormal beat comes very early but it is strongly suggestive of some important degree of atrioventricular block if the premature beat is not very early.

(b) *Ventricular premature beat* If an abnormal excitation wave starts in right or left ventricle it spreads in all directions: sometimes if it starts very late in diastole it meets the normal wave as it comes down through the junctional tissues from the atria and produces with it a composite contraction a condition comparable to that which may also occur in the atria in the case of atrial premature beats.

Usually the premature ventricular wave passes up to the atrioventricular bundle and node but not through it into the atria: the normal atrial contr-

tion begins at this time and thus occurs simultaneously with the abnormal ventricular contraction. The atrioventricular valves being shut as the result of the ventricular premature beat the blood is deflected back from the atria by the normal atrial contraction into the great veins. Since the premature ventricular contraction does not as a rule disturb the normal regular sequence of atrial waves it is followed by a pause which is called compensatory; and the

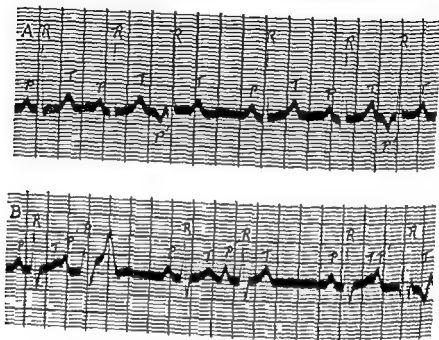


FIG 154 Electrocardiograms (Lead 2) showing atrial premature beats (4) inverted P waves with normal ventricular response (B) upright but premature P waves with abnormal (aberrant) ventricular response varying in degree according to the prematurity of the P waves

dominant rhythm is not disturbed. The interval between the normal heart beat just preceding the premature beat and the ventricular premature beat itself added to the compensatory pause between the ventricular premature beat and the next normal beat gives an interval just equal to that covered by two normal beats when sinus arrhythmia is not present to interfere seriously with the measurements (Figure 155).

Sometimes the ventricular premature beat sends its impulse back through the atrioventricular bundle and node to cause a retrograde atrial contraction; it does then interfere with the dominant sinoatrial rhythm just as an atrial premature beat also interferes with such rhythm. When this happens the pause following the ventricular premature beat is not compensatory. The electrocardiograms of ventricular premature beats are usually bizarre so far as shape of the QRS and T waves are concerned due to the abnormal spread of the impulse resembling somewhat that in bundle branch block. When the impulse has

its origin clearly in the left ventricle and spreads up and to the right the *QRS* wave in Lead 1 is wide and chiefly inverted with high *T* wave and is rather similar to the *QRS* wave seen in normal rhythm with right bundle branch block when it rises clearly in the right ventricle the *QRS* is wide and upwardly directed in Lead 1 with deep *T* resembling the *QRS* seen in normal rhythm with left bundle branch block the *QRS* and *T* waves in Lead 3 are almost

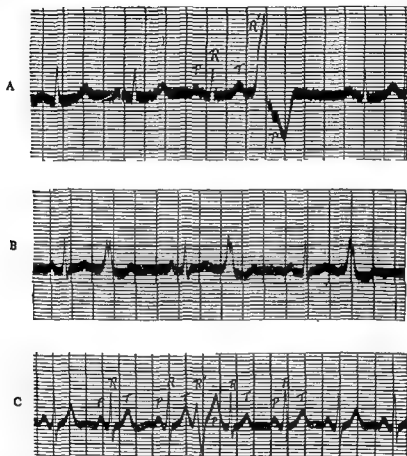


FIG 155 Electrocardiograms (Lead 2) showing ventricular premature beats (A) followed by compensatory pause (B) occurring every other beat to produce a bigeminal pulse and (C) interpolated

always oppositely directed to those in Lead 1 The precordial leads may pick out the origin of the premature beats quickly both by the short interval before the intrinsic deflection and by the upright direction of the complex over the ventricle involved

The separation of right and left ventricular premature beats is of little or no clinical significance

Finally the ventricular premature beat may come so early or the preceding heart rate may be so slow, that the ventricular tissue is no longer refractory when the next normal sinoatrial impulse reaches the junctional tissue the ventricle then responds again in rather quick succession but usually with some delay due to partial atrioventricular block, and with relatively small pressure because of the small amount of blood left in the heart. Such a mechanism is called interpolation of a ventricular premature beat (*interpolated ventricular premature beat*) and is an example of a true extra or additional systole (Figure 155C).

(c) *Atrioventricular nodal premature beat* A premature beat arising in the atrioventricular node or bundle and causing simultaneous contraction of atria and ventricles has an effect like a ventricular premature beat with retrograde atrial contraction and disturbs the dominant rhythm just as does an atrial premature beat. It is however a rare type.

(d) *Sinoatrial nodal (nomotopic) premature beat* A premature beat may also arise rarely in or close to the sinoatrial node (nomotopic) such a beat acts like an atrial premature beat followed by a relatively short pause which is in fact just the length of an interval between normal beats.

*Parasytostole* The subject of the mechanism of premature beats should not be left without mention of the interesting theory of parasytostole which helps to explain the regular occurrence of repeated premature beats in certain cases. It is proposed that a new and abnormal pacemaker is constantly building up stimuli just as is the normal sinoatrial nodal pacemaker but at a different rate. When the refractory state of the muscle and local block about the abnormal pacemaker do not interfere the impulse from the new pacemaker gives rise to premature beats in a regular or irregular relationship to the normal beats. The relative rates of the independent rhythms in parasytostole can be worked out by careful measurements of the tracings. Whether or not the impulse production in such abnormal pacemaker may be of the character of a circus wave is not known.

*Etiology Cause* The cause of a premature beat is an abnormal stimulus production or course in the heart muscle. Certain factors are sometimes responsible for such an abnormal mechanism but the manner of their working is obscure. Direct electrical mechanical or chemical stimulation of an experimental animal's heart will produce premature beats if the stimulation is of sufficient strength that is if it surpasses a certain threshold of responsiveness. Nerve stimulation may also induce premature beats.

In man premature beats have been induced by mechanical stimulation (tapping) of the heart exposed either during operation for some thoracic condition or in very rare cases exposed congenitally. Electrically induced premature beats have also been reported in the case of a man with heart band during drainage of a purulent pericarditis (Barker Macleod and Alexander 1930). Vagus nerve stimulation by carotid pressure in the neck or reflexly by sudden pain anywhere in the body has occasionally elicited premature beats. Forced respiration breath holding overexertion and excitement may induce

them Fatigue indigestion cerebral lesions and hypertension render them more likely or may even cause them on occasion Certain poisons infections and internal diseases are sometimes associated with the appearance of premature beats Individual susceptibility is an important factor as shown by the induction of extrasystoles in some persons and not in others by tobacco tea coffee alcohol and certain drugs Finally heart disease itself favors the occurrence of premature beats and seems occasionally to be a direct cause but many persons with heart disease do not have premature beats and vice versa

*Sex* Both sexes frequently show premature beats the male sex more often as evidenced by a series of 218 cases of my own with a slight preponderance of males (123/95) (White 1926)

*Age* Premature beats may occur at any age they are however most common (in fact almost universal) in old age and rare in infancy and early childhood

*Pathology* There are no specific lesions of heart or nerves associated with premature beats Organic heart disease may or may not be present when it is the myocardium itself is usually normal except for hypertrophy Given a person with premature beats the chances are more than ten to one that no significant structural abnormalities of the heart are discoverable Premature beats are however relatively more numerous in the presence of heart disease than in its absence this is probably to be explained by the strain on the heart muscle resulting from some defect like valvular disease hypertension or coronary disease

It is convenient and of some clinical value to separate premature beats into two main groups namely atrial and ventricular according to their point of origin Ventricular premature beats are much more common than atrial premature beats the ratio being about two to one the ventricular premature beats are less important clinically Atrial premature beats although often occurring without any discoverable cardiac lesions are more likely than are ventricular premature beats to be found in heart disease especially when there is mitral stenosis they then may be the precursors of atrial fibrillation Premature beats arising in the atrioventricular junctional tissues may be classed with ventricular premature beats so far as their clinical significance is concerned

*Symptoms* There may or may not be symptoms with premature beats Probably at least one half of all individuals with this arrhythmia are unconscious of its presence and its discovery in these individuals is an accidental finding on some routine examination Often however the occurrence of the premature beat is felt as a more or less disagreeable sensation due less to the abnormal beat itself than to the pause which follows it to the vigorous thump of the first normal beat after the pause or to the pressure wave forced up into the neck veins from the right atrium at the time of the premature beat this pressure wave results from the contraction of the atria while the ventricles are in systole The sensation may include two or all three of these elements but it is rarely very disagreeable



The occurrence of many premature beats may at first cause much discomfort but if these beats are continually recurring they tend gradually to lose their irritating character and finally they are scarcely or not at all noticed

It is however true that persons with coronary insufficiency may have painful premature beats for the same reason that such individuals with paroxysmal tachycardia may have a status anginosus during the rapid heart action because of the inability of the myocardium to be properly oxygenated during such short diastolic rests quinidine may be very beneficial in such cases this may help to explain its usefulness on occasion in angina pectoris Sometimes in hypersensitive subjects pain may actually be felt with each abnormal contraction and a severe neurosis may result An erroneous diagnosis of angina pectoris has frequently been made in these individuals careful study easily prevents such gross error

When premature beats are so numerous that they interfere with the circulation as in rare instances when they occur in short series or more often than the normal beats dizziness and faintness may result but such symptoms are more likely to be due to an associated nervous reaction If the premature contractions occur as interpolated beats that is, between two normal beats without pause or in short runs the subject may be conscious of a slight fluttering sensation during the period of the three beats occurring in rapid succession

**Signs** The pathognomonic sign of a premature beat is its prematurity which may be discovered by auscultation of the heart itself by palpation of the arterial pulse by inspection of the jugular pulse or by the study of graphic records Feeling the pulse at the wrist is usually the least satisfactory way of detecting the premature beat for two reasons In the first place the abnormal beat is always relatively later in appearance in the pulse cycle at the wrist than at the heart a weak beat traveling more slowly along the arteries than a normal strong beat therefore a premature beat which is but little premature may not be noted as such by the finger on the radial pulse Secondly if the beat is very premature and weak it may not reach the radial artery at all or have sufficient force to be felt the resulting long pause may then be wrongly attributed to partial heart block or to sinus bradycardia rather than to the actual premature beat arrhythmia

Blood pressure studies show almost invariably a lower systolic and smaller pulse pressure with a premature beat than with a normal beat and sometimes there may be no measurable pressure at all Infrequently the premature beat occurs so early that there is not enough intraventricular pressure to raise the semilunar cusps and only a first heart sound is heard sometimes very faintly coming like a third heart sound or a reduplicated second sound of the preceding normal beat (*frustrate contraction*) Occasionally a considerable pulse deficit (the difference between apex and radial pulse rates) may be found if many very early or weak premature beats occur the radial rate may be half the apical in bigeminal rhythm

For complete analysis of a premature beat electrocardiograms are essential mechanical graphic records of arterial venous or cardiac pulsation are in

fenor Usually it is immaterial to know whether a premature beat is of atrial or of ventricular origin or in what part of atrial or ventricular tissue it arises and the discovery of premature beats on auscultation of the heart or on palpation of the pulse may not need further detailed study. It is well however when possible to identify atrial premature beats for they often do presage paroxysmal tachycardia or atrial fibrillation. It is still more important to look for alternation of the pulse that may be revealed by a premature beat and which is of so much greater significance than the premature beat itself (see Chapters 8 and 30).

The differentiation between atrial and ventricular premature beats in the absence of a phlebogram or an electrocardiogram lies in the presence or absence of a compensatory pause. This as a matter of fact is a very rough and unreliable criterion even with graphic records of the arterial pulse. Slight differences of time that may differentiate between a compensatory pause and one that is not fully compensatory are difficult or impossible to measure by finger ear or even sometimes by arteriogram. A more important source of error is the fact that a ventricular premature beat may not be followed by a compensatory pause if it induces a backward-coursing or retrograde atrial contraction as it sometimes does thus breaking up the dominant rhythm. Moreover a ventricular premature beat may be succeeded by atrioventricular nodal escape or by sinus arrhythmia and quickening of rate which occur occasionally to interfere with the application of the principle of the dominant rhythm. At times too an atrial premature beat is followed by a pause that is unusually long either because of succeeding sinus arrhythmia and bradycardia or because the site of abnormal stimulus production in the atrium is so far from the sinoatrial node (for example in the left atrial appendage) that the time expended in traveling back to the node to interrupt its rhythm and the time between the previous normal beat and the premature beat make an interval that is almost indistinguishable from the usual normal time interval.

The electrocardiogram has the great advantage of revealing the presence and type of a premature beat by mere inspection usually without the need of any measurement whatsoever the premature beat is almost always ectopic in origin and so it is of abnormal shape in the electrocardiogram. It is possible by this method of study to determine roughly the site of the abnormal impulse in the atria or in the ventricles. For example a deeply inverted *P* wave usually indicates that the ectopic focus is far from the sinoatrial node and located near the atrioventricular node or in the left atrium although exact localization is as yet impossible (Figure 154). There are also fairly characteristic shapes for the complexes of so-called basal or right and of so-called apical or left ventricular premature beats as already noted above (Figure 155).

**Course and prognosis** A few premature contractions of the heart may occur for a short interval of time (an hour or a day) and never return so far as we know or they may come at more or less frequent intervals once or once an hour once a minute or at frequent often regular intervals the second beat or very rarely they may be more numerous than the

When they occur every second beat they give rise to a coupled rhythm  $\equiv$  bigeminal pulse or if they are too weak to reach the radial pulse a slow regular rhythm at one half the apex rate is felt at the wrist. When they occur every third beat they cause a trigeminal pulse at the apex and ordinarily at the wrist or a bigeminal pulse if they fail to reach the wrist. If they are interpolated there are regular sequences of three beats in rapid succession at the apex and wrist or if the interpolated beats fail to reach the radial pulse there is  $\equiv$  pseudo-alternation every other normal beat following the premature beat being late and small. When the premature beats occur every fourth beat they give rise to  $\equiv$  quadrigeminal pulse at apex and wrist or to  $\equiv$  trimeminal pulse at the wrist if they fail of transmission.

The premature beat is of no clinical importance except in five respects. In the first place individuals with heart disease show relatively a higher incidence and greater frequency of occurrence of premature beats than do those with normal hearts even though the absolute incidence of premature beats is greater in persons without heart disease. Secondly ventricular premature beats occur every other beat or in pairs after every normal beat and those which show by electrocardiogram two or more different shapes and directions of complexes especially if they alternate in shape and direction are evidence of a serious toxic or otherwise irritable state of the myocardium and demand careful study and treatment. Thirdly the premature beat is sometimes a source of great discomfort or fear that must in itself be treated. Fourthly painful premature beats induced by effort may prove to be confirmatory evidence of the presence of coronary insufficiency. And finally the premature beat is now and then directly traceable to some toxic substance like digitalis or tobacco the reduction or omission of which suffices to get rid of the arrhythmia. In the case of digitalis poisoning there may be a bigeminal or coupled rhythm with or without atrial fibrillation due to the regular occurrence of ventricular premature beats the appearance of this arrhythmia in the course of administration of large doses of digitalis indicates that a considerable percentage of  $\equiv$  lethal dose has been given probably close to 75 per cent.

The diagnosis and prognosis of heart disease depend not on the presence or absence of premature beats but almost entirely on other evidence of trouble as Mackenzie so clearly pointed out.

Mackenzie J. *The Extra systole*. Chapter XXVII of *Diseases of the Heart* 3rd ed. London 1913 page 199.

Extra systoles or intermittent heart as they are sometimes called occur so frequently and are viewed by the profession so seriously that it  $\equiv$  necessary to indicate their bearing on the individual's future. Hitherto their cause has been unknown and individuals showing them have been considered unfit for admission into the services military naval and civil and have been considered unsuitable for life premiums and they have been made miserable for life by the vague prognostications of danger and have been subjected to prolonged and quite unnecessary treatment.

"The fact that the occurrence of an extra systole is due to some part of the heart's structure being temporarily more excitable than the normal starting place has led to the idea that it may be an evidence of some disease process. A certain amount of confirmatory evidence for this supposition is found in the fact that people with undoubted disease of the heart do show extra systoles and that extra systoles have sometimes been found to precede the appearance of grave disturbances of the heart's action as auricular fibrillation (Case 51). For these reasons there has been a tendency to view extra systoles as signs of some gravity. If however the subject be studied from a wider and more practical outlook it will be found that extra systoles in themselves are not signs of any specific injury to the heart nor should a prognosis of any gravity be based on their appearance alone. I have watched individuals for over twenty five years who have presented extra systoles sometimes with greater frequency than at other times and these people have led laborious lives and have never shown the slightest symptoms of heart failure or any other evidence of heart impairment. I have had similar experiences with people who have shown all forms of extra systole auricular ventricular and nodal. I have watched young people grow into manhood and lead vigorous lives. I have watched elderly people live beyond 80 years of age in whom I had detected extra systoles at the age of 60 and when they did die the cause of death was not primarily cardiac failure. A short time ago I was consulted by a man aged 69 years whom I found in a fair state of health. He presented auricular extra systoles at frequent intervals and when I remarked upon this he told me that they had been present for over fifty years. Time and again he had submitted to prolonged treatment without avail for the purpose of curing this irregularity. He had oftentimes been made miserable and depressed by the grave prognostications of his medical advisers and had up to the time when I saw him been under the apprehension that he had some obscure heart affection which might prove fatal at any moment.

From such facts as these that healthy men and women may present this form of irregularity it can be gathered that extra systoles in themselves are signs of no significance so far as the efficiency of the heart is concerned.

It may therefore be stated that when the extra systole is the only abnormal sign the prognosis is a favourable one and where it is associated with other signs the prognosis is to be based upon these other signs.

**Treatment.** As a rule premature beats in themselves demand no treatment. Complete reassurance as to their significance can and should almost invariably be given. If there is heart disease or other illness treatment should be directed toward such disease without regard to premature beats unless these abnormal beats cause much discomfort in themselves or unless they are evidence of poisoning by something which can be easily controlled. If there is no evidence of any disease and the premature beats do not occasion much distress reassurance usually suffices to relieve the individual of his fear and much of his consciousness of their presence. It is usually best to tell the patient of the finding of premature beats even when he does not feel them in order to prevent his being unduly alarmed if they are later discovered and taken too seriously by some physician or if their existence becomes evident to the patient himself.

Often the successful treatment of or the spontaneous recovery from what ever disease is present suffices to get rid of the premature beats. For example digitalis which in full dosage may cause premature beats may also actually dispel them either directly or as the result of successful treatment of an associated heart failure. digitalis however much more often causes than dispels premature beats.

If some factor like tobacco alcohol fatigue or constipation appears as responsible for premature beats or is attended by their presence control of this factor generally an easy matter may suffice to abolish the premature beats. Operative correction of some trouble such as gallstones has also been known to be followed by a disappearance of premature beats. Usually however no special measures are effective and the premature beats come and go without possibility of their control.

When premature beats are especially annoying and occasion because of the discomfort they cause a real state of ill health in themselves sometimes amounting even to a partial or complete invalidism careful redirection of the patient's mental and emotional outlook should be undertaken and various drugs may also be tried. The six drugs most likely to help are in their order of choice (1) quinidine sulfate as a 0.2 gm (3 gr) tablet three or four times a day (2) for ventricular (not atrial) premature beats procaine amide (Pro-nestyl hydrochloride) in the dosage of 0.5 to 1.0 gm (one tablet = 0.25 gm) orally every three to six hours (3) potassium salts for example, 2 to 4 gm (30 to 60 gr) of the acetate in 25 per cent solution in peppermint water every 4 to 6 hours especially effective in the case of premature beats due to digitalis intoxication (Sampson and Anderson 1932) (4) bromides preferably  $\frac{1}{2}$  to 1 gm ( $7\frac{1}{2}$  to 15 gr) of triple bromides (of sodium potassium and ammonium) in solution in a few ounces (60 to 90 cc) of water two or three times a day (5) digitalis as a pill of the powdered leaf standard strength (see Chapter 30) 0.06 gm (1 gr) three times a day for a week and (6) papaverine hydrochloride  $1\frac{1}{2}$  gr four times a day. In various cases each one of these remedies has proved effective but in many cases no one of them controls the premature beats. Bromides should be used for short periods of time only because of the hazard of toxic effects. Strychnine given with quinidine has also been recommended when quinidine alone is not effective (Carter and Trant, 1935). The very absence of specific therapy however has flooded the market with remedies of reputed but doubtful value.

**Differential diagnosis.** Premature beats must be differentiated from sinus arrhythmia and heart block. This can in most cases be done easily without an electrocardiogram and in doubtful cases easily with such a record. The usual disappearance of premature beats caused by increasing the heart rate by exercise helps to differentiate a gross arrhythmia due to many premature beats from the absolute arrhythmia of atrial fibrillation which increases on exercise. The clear prematurity of a cardiac contraction followed by a pause longer than the usual interval between two normal heartbeats in an otherwise regular rhythm establishes the diagnosis of a premature beat. Exceptions like interpolated premature beats needing graphic records have been discussed above.

Premature beats are a sign of one type of irritable heart but their occurrence is not to be confused with the so-called irritable heart of soldiers' which in the vast majority of cases has proved to be neurocirculatory asthenia nor is it to be classed as cardiac neurosis although such a condition may be superimposed

And finally angina pectoris is not to be diagnosed when all that a patient complains of is a sharp stabbing pain in the precordium caused by a premature beat

### PAROXYSMAL TACHYCARDIA

Paroxysmal tachycardia is a common disorder of cardiac rhythm closely related to premature beats first mentioned by the ancients in particular Galen but not clearly recognized as a characteristic disorder until Bristowe described it in 1888 it was given its name the following year by Bouveret (1889)

Bristowe J. *On Recurrent Palpitations of Extreme Rapidity in Persons Otherwise Apparently Healthy* *Brain* 1888 X 164

This paper by Bristowe clearly describing paroxysmal tachycardia as a clinical entity for the first time antedated by a year the report by Bouveret in which the term paroxysmal tachycardia was first used The following quotations are of interest

'The subject to which I wish to direct attention is that of extremely rapid pulsation occurring for the most part in intermittent paroxysms of variable duration in hearts structurally and texturally sound and in persons otherwise healthy

That hearts may beat with the extreme rapidity with which I have found them to beat is a fact which I think has been largely overlooked and with which I at any rate had no practical acquaintance until within the last two or three years and yet I feel sure judging from my recent experience that the condition which I am about to discuss is of frequent occurrence and needs only to be looked for intelligently to be recognized in many persons who are regarded as merely nervous and liable to attacks of ordinary palpitation

So far as I know the literature of the subject was until recently limited to the report in the *British Medical Journal* for the year 1866 of three well marked cases the first from the pen of the late Dr Cotton and the others respectively by Dr James Edmunds and the late Sir Thomas Watson Of these cases I need only say that they almost accurately resembled the most striking and typical of the cases which are incorporated in this paper

'The first typical case of the disease which I ever fully recognized was one which I saw in consultation with Dr Wyman of Putney in the early part of 1885 The patient was a fairly healthy looking young married lady who had evidently been liable for some years to attacks of palpitation and was free from structural disease of the heart The attack in which I saw her came on suddenly without apparent cause and after a week left her as suddenly as it had arisen Her pulse varied between 180 and 192 in the minute A few weeks later she had a recurrence of palpitation when the cardiac beats were counted at 246 What seemed to me at the time the most remarkable feature of her case was the apparent absence of distress Had I not known that the patient's heart was beating with extraordinary rapidity it would

never have struck me from watching her and conversing with her that there was anything the matter with her

Bristowe then proceeds to relate eight other cases with or without heart disease and with or without arrhythmia attending the paroxysms of tachycardia. One case was evidently an instance of atrial fibrillation and yet this patient, a man 65 years old, was able to run 3 miles in 20 minutes. His first case described above may of course have had atrial flutter without block when the rate was 246 rather than the usual paroxysmal tachycardia (see Chapter 33). Among the conclusions of the paper the seventh is the most pertinent:

7 As to the real nature of the disease which my paper is intended to illustrate I have little to say. My belief is, as will doubtless have been gathered from all that precedes, that so far as the heart is concerned it is a purely functional disorder, that any actual cardiac disease which may be present in any case must be regarded as accidental, and that the slight hypertrophy and dilatation of the heart which may be found in patients who have suffered from the malady for years are (as I have already remarked) the consequence and not the cause of the palpitation.

**Incidence.** Paroxysmal tachycardia is very frequent but not so universal as are premature beats. Many individuals have short attacks of what they call fluttering of the heart, for which they do not consult a physician, either because the attacks are not sufficiently bothersome or because they are so brief that it would be useless to summon one. If they do seek medical advice the paroxysms usually occur at times when they are not observed by the doctor. Many healthy friends of mine have complained of such attacks lasting usually but a few seconds or minutes and not sufficient in severity or duration to render them of more than passing interest. By special endeavor I have obtained electrocardiograms of some of these attacks when they have been repeated or have been longer than usual, but such success is rare because of the elusive nature of the paroxysms. These observations illustrate the frequency of the condition which is inaccurately represented in any statistical studies at present available, such as my own of a series of 132 cases, 89 (or two thirds) of whom showed no evidence of heart disease (White, 1926).

Ventricular paroxysmal tachycardia, though often serious, is a relatively uncommon type and is found only once to every six cases of atrial paroxysmal tachycardia. In an electrocardiographic series of 103 cases of paroxysmal tachycardia at the Massachusetts General Hospital the origin of the abnormal rhythm was clearly in the atria in 80 and clearly in the ventricles in 14.

**Mechanism (abnormal physiology).** Paroxysmal tachycardia appears to be due to a rapid, usually regular, production of waves of excitation and contraction at some point in the atrial or ventricular muscle, generally outside the normal sinoatrial nodal pacemaker, although rare instances of nodotopic or sinoatrial paroxysmal tachycardia have been reported. Electrocardiographic study shows that the separate excitation waves closely resemble those of atrial or ventricular premature beats. The exact mechanism of production of such a rapid succession of premature contractions is not clear. Theories have ascribed it to the rapid building up of a stimulus, as in the case of normal sino-

atrial tachycardia which seems most likely or to constant circus movement of an excitation wave once started or to some other unknown cause. Its main characteristics are its sudden onset and offset, its rapid rate (120 to 200 or rarely somewhat more usually 160 to 180) and its tendency to great regularity. In the rare paroxysmal tachycardia of infancy the heart may attain an extraordinarily rapid rate of beating even at 300 or more. The fastest rate that I knew of at the time of the second edition of this book was in an infant whose heart rate was 312, the result of either atrial paroxysmal tachycardia with bundle branch block or ventricular paroxysmal tachycardia; the infant died of bronchopneumonia, erysipelas, empyema and meningitis but showed no abnormality of the heart at autopsy (Lyon 1937). In 1937 Campbell reported three interesting cases of extremely rapid heart rates in infancy (300, 274 and 266 respectively), two of whom had congestive heart failure during their paroxysms but recovered completely. Later Hubbard published his important study of nine infants with paroxysmal tachycardia; their rates were 270, 300, 274, 300, 260, 290, 305, 270 and 220 respectively (Hubbard 1941). At the time of the third edition of this book (1944) I stated that I had seen electrocardiograms of a few very young infants with heart rates of 300 to 310 and had noted the remarkable case of a 10 day old infant with a heart rate of 345 reported by Puglisi (1939). Since then even faster rates have been noted, for example 365 per minute, unrecognized until just before death in the case of an infant (Silverman and Race 1949).

(a) *Atrial paroxysmal tachycardia.* Atrial paroxysmal tachycardia (Figure 156) is by far the most common and least important type of paroxysmal tachy-

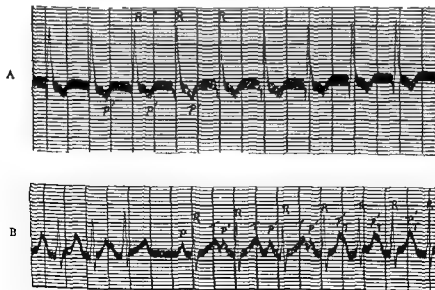


FIG 156 Electrocardiograms (Lead 2) showing atrial paroxysmal tachycardia (A) The usual mechanism (B) an unusual variation with short runs of tachycardia and varying rate



cardia occurring about six times more often than the ventricular type. It is usually very regular at a rate of 160 to 180, but on rare occasions there may be a gradual onset, gradual offset, and some slight arrhythmia during its course. The abnormal contractions are usually represented in the electrocardiogram by inverted *P* waves in Leads 1 and 2, diphasic *P* waves in Lead 3, and inverted *P* waves in the precordial leads, but sometimes the *P*s are upright with abnormal contour. The appearance of these ectopic atrial complexes may vary considerably with change in position of the heart due to forced breathing; the inverted *P* waves in Lead 2 during quiet breathing, for example, becoming diphasic or even upright on deep inspiration, resulting from the changed relationship of the position of the ectopic focus and that of the heart. The abnormal *P* waves in atrial paroxysmal tachycardia are usually followed by normal ventricular responses at the same rate, but occasionally when the rate is very rapid there may be temporary atrioventricular or intraventricular block, so that 2 to 1 partial block or left or right bundle branch block may appear as a transient associated functional disorder of little or no clinical importance in itself. Rarely an atrial paroxysmal tachycardia may be interrupted by a ventricular premature beat.

(b) *Ventricular paroxysmal tachycardia*. Paroxysmal tachycardia of ventricular origin (Figure 157) is an important, frequent, and usually a serious disturbance of rhythm, similar in other characteristics to atrial paroxysmal tachycardia, except that it tends to be somewhat less regular in its rhythm. The arrhythmia, although obvious on electrocardiographic measurement, is evident clinically in only about half of the cases on close examination. The shape of the ventricular complex of the electrocardiogram is exactly like that of a ventricular premature beat, but in a few instances there is a variation in shape from beat to beat. In the most marked cases an alternate reversal of direction with slight alternation of time intervals (Figure 157C). When an alternating bidirectional character of the ventricular complexes of ventricular paroxysmal tachycardia is seen, the condition is invariably a serious one, usually terminal. The fundamental sinoatrial rhythm may or may not be disturbed by a paroxysm of ventricular tachycardia; usually it is at least quickened, even though it may remain independent. Sometimes retrograde atrial responses follow each or every other abnormal ventricular beat in this variety of tachycardia. On occasion atrial fibrillation, and very rarely atrial paroxysmal tachycardia, may coexist with ventricular paroxysmal tachycardia. The differentiation of abnormal ventricular tachycardia into right ventricular and left ventricular types has been suggested, as in the case of ventricular premature beats (see Chapter 9 and the first part of the present chapter), but as yet the clinical value of such differentiation has not been shown.

(c) *Atrioventricular nodal paroxysmal tachycardia*. This is very rare. It has the relatively unimportant clinical significance of atrial paroxysmal tachycardia and a mechanism somewhat similar to that of ventricular paroxysmal tachycardia with regular retrograde atrial response, although in rare instances

the atrial contraction may precede the ventricular even when the impulse starts in the atrioventricular node

Electrocardiographic records are needed to differentiate clearly the different types of paroxysmal tachycardia a phlebogram if it happens to show the onset or offset of a paroxysm gives a certain amount of information but not clear enough proof

A very interesting small group of cases of paroxysmal tachycardia atrial mostly but sometimes ventricular consists of otherwise healthy young people who show by electrocardiogram either constantly or temporarily short *P R* intervals This syndrome will be discussed further in Chapter 34 but a clearer

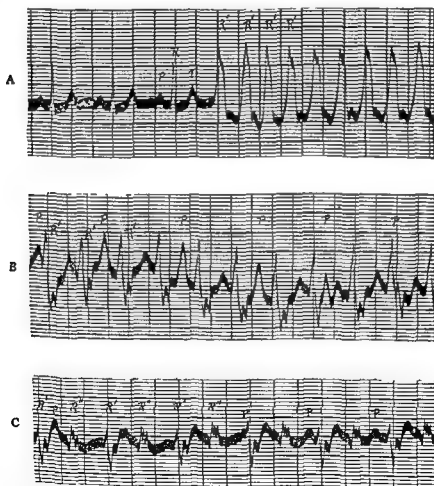


FIG 157 Electrocardiograms (Lead 2) showing ventricular paroxysmal tachycardia (A) onset of the usual type (B) with *P* waves clearly seen superimposed on the *QRS* and *T* waves and quite independent of them and (C) with ventricular complexes alternating in direction (also called "bidirectional")

understanding of the mechanism of this syndrome might throw light on the mechanism of paroxysmal tachycardia itself

**Etiology Cause** Just how the abnormal mechanism of paroxysmal tachycardia is initiated is not known but certain causative factors are known. Conditions responsible for premature beats are likewise responsible for atrial paroxysmal tachycardia. Such factors are fatigue, sudden exertion, indigestion, tobacco, alcohol, digitalis poisoning, infection, and heart disease. As in the case of premature beats, heart disease is more often absent than present when there is atrial paroxysmal tachycardia, though here again a diseased heart is more often affected by paroxysmal tachycardia than is a normal heart. Often there is no known or discoverable cause for atrial paroxysmal tachycardia.

Ventricular paroxysmal tachycardia is found as a rule, but not always, in the presence of organic heart disease of serious type, and can be rapidly fatal if the electrocardiogram shows alternating direction of the complexes. Digitalis intoxication has been associated in a number of the fatal cases on record. In a few instances ventricular paroxysmal tachycardia occurs with little or no evidence of organic heart disease.

**Sex** Both sexes are probably affected about equally by paroxysmal tachycardia of either atrial or ventricular type. In the series of my own of 132 cases noted above the females were preponderant in the ratio of 82 to 50, but in another electrocardiographic series of 80 cases of atrial paroxysmal tachycardia 42 were male and 38 were female, while of 13 cases of ventricular paroxysmal tachycardia proved electrocardiographically 8 were male and 5 were female.

**Age** Atrial paroxysmal tachycardia is common after childhood but rare in infants and young children. Ventricular paroxysmal tachycardia is rare at any age, is commonest in the serious heart disease of later life.

**Family incidence** It is not uncommon for paroxysmal tachycardia to occur in several members of the same family.

**Pathology** There is no pathologic condition in the heart characteristically found with paroxysmal tachycardia; most cases of this disturbance of rhythm have apparently perfectly normal hearts. There are, however, certain chances which favor paroxysmal tachycardia. Mitral stenosis is not infrequently accompanied by atrial paroxysmal tachycardia before the onset of permanent atrial fibrillation, but paroxysmal atrial fibrillation which also occurs in mitral stenosis must be differentiated from atrial paroxysmal tachycardia. The heart in thyrotoxicosis may be affected by either atrial paroxysmal tachycardia or paroxysmal atrial fibrillation, but more commonly by the latter. And finally, cardiac infarction is likely to be found responsible in the more serious cases of ventricular paroxysmal tachycardia.

**Symptoms** Usually the person affected is conscious of the disturbance of rhythm, but in rare cases a paroxysm long or short may pass unnoticed except by the observer; this happens in insensitive persons or in individuals who are too ill to appreciate this complication. The general complaint is of a regular rapid palpitation or of a disagreeable sensation of fluttering in the

chest in the region of the heart. The sensation may be widely referred over the body so that the vessels seem to pound in head and arms, abdomen and legs. A fullness in the neck is often complained of due to the transmission of the pulsation to the jugular veins. There may or may not be associated dyspnea and heartache due in part and in all probability chiefly to nervousness and fear in sensitive persons and representing a kind of neurocirculatory asthenia but dyspnea may also be due to cardiac fatigue in persons with hearts already weakened or overburdened or occur after very long paroxysms lasting for days. Angina pectoris has sometimes been noted during the paroxysms in persons with coronary heart disease to start with giving rise to a *status anginosus* until the paroxysm subsides and symptoms of congestive failure with engorgement of liver and lungs are occasionally produced by long paroxysms of tachycardia in patients with heart disease and rarely in persons without heart disease. With an extremely rapid rate in paroxysmal tachycardia the brain may receive little blood and faintness, dizziness and even syncope may ensue. If the pulse is faint or absent and unconsciousness and convulsions result from the extreme tachycardia the condition may simulate the Morgagni-Adams-Stokes syndrome of high grade heart block. An occasional symptom during or following paroxysmal tachycardia is increased frequency or increased amount of urination doubtless a nervous reflex in large part.

**Signs.** The pathognomonic evidence of paroxysmal tachycardia is electrocardiographic (Figures 156 and 157) but any regular rapid rate of 120 to 200 per minute observed clinically to start abruptly and to stop abruptly and lasting usually a few minutes (with a range from a few seconds to several days) may be reasonably diagnosed as paroxysmal tachycardia without the need of graphic records. A striking feature of paroxysmal tachycardia is the uniformity of rate as compared with ordinary sinoatrial tachycardia which varies in rate under various conditions such as exercise, change of position, carotid pressure, deep breathing and digitalis therapy. A variation of a few beats per minute may however occur from time to time even in paroxysmal tachycardia especially of the ventricular type and especially under the influence of quinidine.

Aside from the tachycardia there is usually no other sign. There may or may not be evidence of chronic heart disease and enlargement. Except when the heart is exhausted or diseased it is usually found by roentgen ray examination during a paroxysm to be decreased slightly or moderately in size below the normal. This is due to the fact that the rapid rate prevents full normal diastolic dilatation. Sometimes even in the case of normal hearts prolonged paroxysmal tachycardia may cause cardiac dilatation which is evident by roentgen ray. The blood pressure is usually normal or somewhat decreased during a paroxysm and the pulse small due to the rapid rate. At times during a very rapid heart rate or after a long paroxysm alternation of the pulse occurs due doubtless to myocardial fatigue (Figure 33 page 162) pulsus alternans is not then the serious sign that it is with slower pulse rates; the faster the heart rate the less important the pulsus alternans. It is probable

that a healthy heart beating at a rate of nearly 300 per minute should normally show alternation of the pulse. The occasional development of intraventricular block at very rapid heart rates is likewise a more or less 'normal' physiologic condition.

Signs of congestive failure may be found to begin or to increase in cases of heart disease during paroxysms of tachycardia. Very rarely a long paroxysm at a very fast rate may give rise to signs of failure even in the absence of heart disease; this is especially true of the extreme tachycardias in infants whose hearts and livers may become very large, shrinking rapidly when the attacks cease (Hubbard 1941).

Electrocardiographic study is helpful during a paroxysm of tachycardia, particularly in differentiating the atrial type from the ventricular and in excluding atrial flutter. Following a prolonged or very severe paroxysm of tachycardia the *T* waves of the electrocardiogram may become inverted even for some days and even in the absence of heart disease due evidently to myocardial fatigue (Campbell 1942).

**Course and prognosis.** Atrial paroxysmal tachycardia is usually unimportant. It is a transient disturbance, as a rule lasting but a few seconds or a few minutes and only rarely more than a few hours, sometimes occurring but once and sometimes repeatedly over a short space of time (a few days or weeks). It tends to recur off and on through life but often at long intervals (years for example). It generally neither shortens life nor limits activity but in some cases it necessitates rest during the paroxysms and if the paroxysms are long or numerous there may be much crippling; in a few cases complete invalidism may result. Heart failure and death are very rarely induced by paroxysmal tachycardia in a patient with heart disease except in the case of atrial paroxysmal tachycardia complicating marked mitral stenosis or other pathologic condition where the cardiac reserve is low and failure easily induced and in the case of ventricular paroxysmal tachycardia which may be itself a terminal condition rather than a cause of death.

Like premature beats, paroxysmal tachycardia of atrial origin cannot be considered to be a diagnostic or prognostic sign of any importance. Diagnosis and prognosis must be based on other findings. Paroxysmal tachycardia of ventricular origin, on the other hand, must be considered serious until proved unimportant.

**Complications.** Only rarely a paroxysmal tachycardia attended by complications. The most important ones are (1) congestive heart failure in the presence of pre-existing heart disease and even without previous heart disease especially if, as in infants, the heart rate is excessively fast (300 more or less per minute); (2) myocardial infarction in the presence of a high degree of coronary artery narrowing and due to the abrupt drop in effective coronary blood flow; (3) the temporary status anginosus in coronary heart disease without actual infarction; (4) syncope which may be either a nervous reaction, the result of marked decrease in cerebral blood flow during the paroxysm or due to a transient total cardiac standstill at the end of the paroxysm and before

the resumption of normal rhythm and (5) death from evolution of ventricular tachycardia into ventricular fibrillation

**Treatment** Usually no treatment of atrial paroxysmal tachycardia is needed if the attacks are brief and rare that is not more than ten or fifteen minutes long or oftener than once a month. If the paroxysms are long or frequent, however or even if they are short and infrequent but disagreeable an attempt should be made to abolish them.

The treatment consists of therapy directed to stop the individual attack and of therapy to prevent a recurrence of paroxysms.

(a) *Therapy of an attack of atrial paroxysmal tachycardia* should be as simple as possible and not include the administration of a great variety of unreliable remedies to which recourse is frequently had.

The following procedure has been found in the hands of experienced observers to be a good one to adopt. In the first place it is usually wiser for the patient to remain quiet during the paroxysm seated or recumbent than to continue full or even partial activity although it is possible and sometimes necessary to complete a task or effort in progress at the time of the onset of the paroxysm. Usually the paroxysms are shorter during rest than during exercise but occasionally the reverse is true and if so exercise should be prescribed especially calisthenic motions of arm stretching or body bending which may cause an abrupt cessation of the attack. Even in the resting position certain postures are sometimes uniformly or frequently effective in stopping paroxysms for example leaning forward in a chair with the head low or lying with the head lower than the rest of the body.

If the paroxysm does not stop quickly after the patient has assumed the most satisfactory position it is always worthwhile to try the effect of stimulation by firm carotid sinus pressure with the tips of two or three fingers for from five to thirty seconds high on the right side of the neck over the fullest carotid pulsation. If pressure on the right side is ineffective the same procedure may be tried on the left side or moderately firm pressure with the finger tips may be exerted on either eyeball with the eye closed (oculocardiac reflex method). In about 10 per cent of all cases the reflex vagal effect of these pressure methods or of position changes are effective and the paroxysms stop abruptly and dramatically usually with great relief to the patient. Since these procedures are easy and with rare exceptions safe they are always to be recommended. Right carotid sinus pressure should be tried before the left and before ocular pressure since it is more likely to be effective and since pressure on the neck is less disagreeable than that on the eyeballs. In very rare instances carotid sinus pressure has been followed by cerebral vascular accidents such as thrombosis but I myself have never encountered such sequelae. Various other mechanical and reflex measures have been utilized in individual cases with occasional success such as the induction of vomiting, firm abdominal pressure, application of an ice bag over the precordium, drawing out the tongue, forced respiration and the Valsalva or Muller experiments (the former consisting of an attempt to expire forcibly with the glottis closed after

a deep inspiration and the latter being an attempt to inspire forcibly with the glottis closed after a deep expiration) but these measures are not to be routinely recommended. Often the paroxysm ceases spontaneously and the particular measure being tried at the time may unjustly be credited with the cure.

Drug therapy of a paroxysm is often unreliable. The best all around drug to try first is quinidine which may be employed if a paroxysm is long (more than an hour), distressing or exhausting. Quinidine sulfate in tablet or powder form may be given by mouth (0.4 gm or 6 gr every two hours for five doses under observation) this oral therapy has proved to be effective in cutting short the paroxysms in frequent cases in my experience and in that of others but it cannot always be relied upon. In patients severely ill with ventricular (and in fact also atrial) paroxysmal tachycardia who have failed to respond to quinidine by mouth or who are too nauseated to take it a convenient and effective method of treatment is the subcutaneous injection of 1 gm (7½ gr) of quinidine lactate or hydrochloride (injectable) every 2 hours until the paroxysm ends or toxic symptoms of cinchonism appear. Intravenous injection of 0.2 to 0.4 gm of quinidine lactate or sulfate directly and repeated every four hours as needed or in the form of a drip (3.3 gm or 50 gr dissolved in 500 cc normal saline or in 5 per cent glucose solution) administered until there is an effect has also been recommended. Occasionally striking benefit has been reported from this measure but it is simpler, safer and about as effective to give the drug by mouth or to use quinidine salts intramuscularly.

Another drug that has been used to control paroxysmal tachycardia especially by Starr and his associates (1933) is Mecholyl (acetyl β methylcholine chloride) which acts through its stimulation of the parasympathetic nerves (including the vagus). The Mecholyl was successful in from one half to twelve minutes in abolishing twenty four attacks of paroxysmal tachycardia ventricular or atrial in nine patients of Starr's when injected subcutaneously in the dosage of 20 to 30 mg. It may however have untoward effects consisting of the production of vomiting, dyspnea, asthma (stopped by atropine), pain, marked fall of blood pressure and heart block. Atropine sulfate (1 mg or 1/60 gr in solution) should be at hand to inject immediately in case of toxic symptoms. Recently Mecholyl in larger dosage 200 to 300 mg has been found to be effective when given intranasally (Nathanson and Tober 1948).

More recently revived as drug therapy to induce vigorous central vagal stimulation by means of marked nausea is the administration of syrup of ipecac by mouth 8 to 16 cc (2 to 4 drachms) at a dose repeating it as needed to build up a vagal stimulation marked enough to stop the paroxysm of tachycardia or at least to induce vomiting. This measure is usually effective and not dangerous but it is disagreeable and to be reserved for the most severe cases.

If a patient is in much distress and the paroxysm continues despite the measures described above various other drugs may be tried. Bromides may be administered 1 gm (15 gr) of the triple bromides every four hours for a few doses as needed or rarely morphine 0.01 to 0.015 gm (¼ to ¼ gr) intra-

venously or subcutaneously it is however very important to avoid using morphine except in the rarest cases of severe prolonged pain pulmonary edema or shock or obstinate ventricular tachycardia because of the very real possibility of establishing morphinism in the treatment of this disorder which is so often recurrent. Also bromides should be used for only short periods of time because of the hazard of toxic effects. In a few cases digitalis intravenously (two or three doses of 0.2 to 0.4 mg of digitoxin or of 0.1 to 0.5 gm of Digifolin Digalen or similar preparation for intravenous administration in 10 per cent solution at intervals of four hours) or strophanthin intravenously 0.5 to 0.25 mg or (1/120 to 1/240 gr) once has been followed by a rapid cessation of a paroxysm of tachycardia but often this treatment is ineffective it should be tried only if other measures in the control of an obstinate attack have failed or if there are symptoms and signs of congestive failure. In infants with prolonged paroxysmal tachycardia at excessive rates Hubbard found that digitalis (Digifolin) in the dosage of 0.1 to 0.3 gm daily for one or two days was usually very effective and should be used at once in preference to any other treatment (Hubbard 1941).

Another therapeutic measure which has been tried and recommended in cases of intractable paroxysmal tachycardia is the injection of novocaine (procaine) and of alcohol in the stellate ganglion left or right (Coleman and Bennett 1938 Leibovici et al 1939)—this procedure needs further testing before adoption since it is still only in the experimental stage. Somewhat related has been the successful control of disturbing paroxysmal tachycardia occurring during cyclopropane anesthesia by the intravenous injection of procaine (0.1 per cent solution) (Kraft 1947). Finally magnesium sulfate in 10 per cent solution by slow intravenous injection (2 gm in 5 minutes) has been recommended.

(b) *Therapy of an attack of ventricular paroxysmal tachycardia* A paroxysm of ectopic ventricular tachycardia is as a rule much more serious than a paroxysm of ectopic atrial tachycardia and therefore demands almost invariably emergency treatment. This consists of the use of quinidine or of procaine amide (Pronestyl). Quinidine may be given in the form of the sulfate by mouth dosage of 0.4 gm (6 gr) to be repeated in one hour and again in another hour if the attack is still in progress unless the situation is very urgent under which conditions the drug should be given intramuscularly in the form of the lactate gluconate or hydrochloride (injectable). Ampoules of solutions of these salts have been prepared for intramuscular use 0.4 to 0.6 gm (6 to 9 gr) should be given and repeated at two hour intervals for several doses if necessary. Although intravenous medication has been used it is less desirable because of its toxic effects. Sedatives and even narcotics may be needed also especially if the ventricular tachycardia induces severe dyspnea with pulmonary edema or status anginosus.

Recently procaine amide (Pronestyl hydrochloride) has been introduced both in the treatment and prevention of paroxysms of ventricular tachycardia. It is the most effective therapy yet found and is given in the dosage of 0.5 to



10 gm orally or intravenously the latter in 5 to 10 cc solution. It can be repeated at two hour intervals as needed in direct therapy and every three to six hours orally as a prophylactic.

(c) *The prevention of paroxysms of tachycardia* is just as uncertain as is the treatment of an individual attack. In the first place possible factors responsible for the occurrence of the paroxysms should be sought and eliminated. Such factors may be fatigue, overuse of tobacco, tea or coffee, constipation, indigestion, overeating, overexertion, focal infection, and heart failure. In the second place there are certain positive measures which are sometimes effective. Quinidine sulfate in daily rations constantly or at intervals (0.2 gm or 3 gr. in tablet or powder form three or four times a day) is frequently beneficial, reducing or abolishing the paroxysms in about half the cases. In rare individuals when the quinidine is ineffective, digitalization may work well; at least it is worth trying in obstinate cases in the dose of 0.06 gm (1 gr.) of the powdered leaf (of the new international and U.S.P. standard strength—see Chapter 29) in pill form three times a day for a week for an adult of average size; then if effective the digitalis may be continued in daily rations of 0.06 gm (1 gr.) for as long as necessary. It is to be remembered that toxic doses of digitalis may themselves cause paroxysmal tachycardia, especially of ventricular type. Potassium salts have also been recommended for obstinate tachycardia, as in the case of premature beats. Stempien and Katz (1942) for example have advised giving 1 or 2 gm of potassium chloride or acetate every two to four hours to supplement or reinforce the action of quinidine. Bromide therapy, 1 gm (15 gr.) of the triple bromides once or twice a day may be useful in relieving the discomfort and worry caused by the paroxysms, even if not in reducing the number and duration of the paroxysms themselves. Finally thoracic sympathectomy has been introduced to prevent or to decrease the incidence of obstinately recurrent paroxysmal tachycardia but with as yet inconclusive results.

Reassurance is always an important part of the treatment and may itself suffice to get rid of the major part of the patient's unfavorable reaction to the attacks. Moreover daily exercise in the open air may have a salutary influence on an irritable heart.

**Differential diagnosis.** Paroxysmal tachycardia must be differentiated from extreme sinoatrial tachycardia, atrial flutter, and atrial fibrillation. Its steady rapid rate and sudden onset and offset distinguish it from sinoatrial tachycardia. Its short duration (seconds, minutes, or hours rather than days, weeks, months, or years), the slower atrial rate (100 to 200 rather than 200 to 400) and the failure of atrioventricular block to be an almost constantly associated condition distinguish it from atrial flutter. Its regularity of rhythm distinguishes it from atrial fibrillation. To differentiate atrial from ventricular paroxysmal tachycardia with certainty an electrocardiogram is necessary, though clinically a slight arrhythmia favors the diagnosis of the ventricular type.

Finally the abruptness of the paroxysms of tachycardia may now and then result in confusion with heart attacks other than arrhythmias, especially

angina pectoris, coronary thrombosis and acute dyspnea careful analysis should easily prevent such confusion: except perhaps in rare cases actually suffering from two different kinds of heart attacks occurring simultaneously (in which case the tachycardia may induce anginal pain or acute heart failure) or occurring alternately

## BIBLIOGRAPHY

### PREMATURE BEATS AND PAROXYSMAL TACHYCARDIA

SEE ALSO GENERAL REFERENCES FOLLOWING CHAPTER 2 REFERENCES UNDER CHAPTER 29 ESPECIALLY MACKENZIE 'DISEASES OF THE HEART' LEWIS MECHANISM AND GRAPHIC REGISTRATION OF THE HEART BEAT AND WENCKEBACH AND WINTERBERG 'DIE UNREGELMÄSSIGE HERZTÄTIGKEIT' AND REFERENCES UNDER QUINIDINE THERAPY IN THE BIBLIOGRAPHY OF CHAPTER 33

#### Premature Beats

- Barker P S Macleod A G and Alexander J "The Excitatory Process Observed in the Exposed Human Heart" *Am Heart J* 1930 V 720
- Brow G R Lone C L H and Beattie J "Irregularities of the Heart under Chloroform Their Dependence on the Sympathetic Nervous System" *JAMA* 1930 XCV 715
- Carter J B and Trant E F Quinidine and Strychnine in Treatment of Premature Contractions *Am J M Sc* 1935 CLXXXIX 706
- Castleden L I M Effect of Potassium Salts on Cardiac Irregularities *Brit M J* 1941 I 7
- Hering H E "Zur experimentellen Analyse der Unregelmässigkeiten des Herzschlages" *Pflügers Arch f d ges Physiol* 1900 LXXXII 1
- Levy A G The Genesis of Ventricular Extrasystoles Under Chloroform with Special Reference to Consecutive Ventricular Fibrillation *Heart* 1914 V 299
- Mackenzie J "The Extra systole" Chapter XXVII of *Diseases of the Heart* 3rd ed London 1913 page 199
- Myers M M and White P D Interpolated Contractions of the Heart with Especial Reference to Their Effect on the Radial Pulse *Arch Int Med* 1921 XXVII 503
- Rothberger C J De la parasystole *Traité d'electrocardiographie clinique* edited by Veil and Codina Altes Paris 1928
- Sampson J J Alberton E C and Kondo B The Effect on Man of Potassium Administration in Relation to Digitalis Glycosides with Special Reference to Blood Serum Potassium the Electrocardiogram and Ectopic Beats *Am Heart J* 1943 XXVI 164
- Sampson J J and Anderson E M The Treatment of Certain Cardiac Arrhythmias with Potassium Salts *JAMA* 1942 XCIX 2257
- White P D Observations on Functional Disorders of the Heart *Am Heart J* 1946 I 527
- Zander E Zur Frage von der Extrasystole als Interferenzerscheinung mehrerer Herzrhythmen. *Acta med Scandinav* 1927 LXVII 1

#### Recent References (1944-1950)

- Langendorf R and Mintz S S Premature Systoles Originating in the S A Node *Brit Heart J* 1946 VIII 178
- Porter W H Probably Grave Significance of Premature Beats Occurring in Angina Pectoris Induced by Effort *Am J M Sc* 1948 CCXVI 509
- Praet H J Abolition of Extra Systoles in the Perfused Isolated Rabbit Heart by Procaine and Monocaine Hydrochlorides *Federation Proc Fed Am Soc Exper Biol* 1948 VII 250
- Sensenbach W and Bue R M Jr Persistent Ventricular Bigeminal Rhythm in Apparently Normal Hearts *Am J M Sc* 1946 CCXI 332

## Paroxysmal Tachycardia

- Barker P S Wilson F N and Johnston F D "The Mechanism of Auricular Paroxysmal Tachycardia" *Am Heart J* 1943 XXVI 435
- Barker P S Wilson F N Johnston F D and Wishart S W "Auricular Paroxysmal Tachycardia with Auriculoventricular Block" *Am Heart J* 1943 XXV 765
- Bouveret L "De la tachycardie essentielle paroxystique" *Rev d méd Paris* 1889 IX 753 (This paper contains the first employment of the term paroxysmal tachycardia.)
- Boyd L J and Scherf D "Magnesium Sulfate in Paroxysmal Tachycardia" *Am J M Sc* 1943 CCVI 43
- Bristowe J S "On Recurrent Palpitation of Extreme Rapidity in Persons Otherwise Apparently Healthy" *Brain* 1887 X 164 (This paper contains the first clear account of typical cases of paroxysmal tachycardia.)
- Campbell M "Paroxysmal Tachycardia in Infants" *Guy's Hosp Rep* 1937 LXXXVII 205
- Inversion of the T Waves After Long Paroxysms of Tachycardia *Brit Heart J* 1942 IV 49
- Campbell M and Elliott G A "Paroxysmal Tachycardia: Aetiology and Prognosis of One Hundred Cases" *Brit M J* 1939 I 123
- Cohn A E and Fraser F R "Paroxysmal Tachycardia and the Effect of Stimulation of the Vagus Nerves by Pressure" *Heart* 1913 V 93
- Coleman E P and Bennett D A "Injection of the Right Stellate Ganglion with Alcohol in Paroxysmal Tachycardia" *Surg Gynec and Obst* 1938 LXVII, 349
- Cooke W T and White P D "Prognosis of Paroxysmal Tachycardia and Paroxysmal Auricular Fibrillation" *Brit Heart J* 1942 IV 153
- Decherd G M Jr Herrmann G R and Schwab E H "Paroxysmal Supraventricular Tachycardia with A V Block" *Am Heart J* 1943 XXVI 446
- Finkle G E "Treatment of Paroxysmal Tachycardia with Apomorphine" *Kansas M Soc J* 1939 XL, 372
- Géraudel E and Mouquin M "Arrêt brusque d'une longue crise de tachycardie paroxystique par injection intraveineuse d'un sel de quinine" *Paris méd* 1918 18 Année (Partie méd.) p 26
- Hubbard J P "Paroxysmal Tachycardia and Its Treatment in Young Infants" *Am J Dis Child* 1941 IXI 687
- Leibovici R et al "Accès post-opératoire grave de tachycardie paroxystique traité avec succès par la novocainisation du ganglion stellaire gauche" *Presse méd* 1939 XLVII 83
- Lyon J A "Excessively Rapid Heart Rates: Report of a Case with Autopsy" *JAMA* 1937 CVIII 1393
- Marvin H M and White P D "Observations on Paroxysms of Tachycardia" *Arch Int Med* 1922 XXIX 403
- Morgan P W "The Management of Paroxysmal Tachycardia Including the Use of Mecholyl" *Ann Int Med* 1943 XIX 780
- Otto H L and Gold H "Auricular Paroxysmal Tachycardia: The Effect of Epinephrine Quinine Quinidine Atropine and Digitalis" *Am Heart J* 1926 II 1
- Puglisi A "Tachicardia paroxistica en un recién nacido" *Arch argent d pediat* 1939 XI 3
- Sprague H B and White P D "Heart Block During Auricular Paroxysmal Tachycardia (Clinical Observations on Three Cases)" *M Clin North America* 1924-5 VIII 1855
- Starr I Jr "Acetyl B Methylcholin III Its Action on Paroxysmal Tachycardia and Peripheral Vascular Disease With a Discussion of Its Action in Other Conditions" *Am J M Sc* 1933 CLXXXVI 330
- "Acetyl B Methylcholin IV Further Studies of Its Action in Paroxysmal Tachycardia and in Certain Other Disturbances of Cardiac Rhythm" *Ibid* 1936 CXCII 710
- Walsh H J and Sprague H B "Paroxysmal Tachycardia in a Child Treated with Acetyl Beta Methylcholine Chloride (Mecholyl)" *Am Heart J* 1940 XX 111
- Weiss S and Sprague H B "Vagal Reflex Irritability and Treatment of Paroxysmal Auricular Tachycardia with Ipecac" *Am J M Sc* 1937 CXCIV 53

- White P D and Stevens H W "Ventricular Response to Auricular Premature Beats and to Auricular Flutter" *Arch Int Med* 1916 XVIII 712
- Wolff L, Parkinson, J and White P D "Bundle Branch Block with Short P R Interval in Healthy Young People Prone to Paroxysmal Tachycardia" *Am Heart J* 1930 V 685

*Recent References (1944-1950)*

- Almuring, M M Eley M C and Massell B F Paroxysmal Auricular Tachycardia Report of a Case with Persistent Ectopic Auricular Pacemaker without Sinoauricular Node Activity *Am Heart J* 1950 XL 468
- Jurkovic, V Paroxysmální tachykardie zastavena oboustranným znecltním hv zdicovité uzliny (Ganglion stellatum) " *Praktický lékař* Prague 1950 XXX 57
- Kraft, K. A "Intravenous Procaine" *Canad M A J* 1947 LVII 350
- Michel J, Johnson A D, Bridges W C, Lehmann, J H, Gray F, Field L and Green D M "Arrhythmias During Intracardiac Catheterization" *Circulation* 1950 II 740
- Parkinson J., and Papp C "Repetitive Paroxysmal Tachycardia" *Brit Heart J* 1947 IX 241
- Schaffer A. I, Steinman R and Scherf D "Intravenous Procaine Its Effect on the Human Electrocardiogram and on Cardiac Arrhythmias" *Cardiologia* 1950 XVI 347
- Schwartz, W B., and Levine S A "A Case of Paroxysmal Auricular Tachycardia with Block Present Almost Continuously for Twenty five Years" *Circulation* 1950 I 936
- Segers M, Lequime J and Denolin H "Effect of Intravenous Injections of Acetylcholine in Man II Control of Crises of Paroxysmal Tachycardia" *Acta med scand* 1945 CXXII 281
- Silverman J J and Race O M Paroxysmal Tachycardia with Ventricular Rate of 365 Per Minute" *Am Heart J* 1949 XXXVII 1139

**Ventricular Paroxysmal Tachycardia**

- Allen C R, Stutzman J W and Meek W J "Production of Ventricular Tachycardia by Adrenalin in Cyclopropane Anesthesia" *Anesthesiology* 1940 I 158
- Barker P S Ventricular Tachycardia During an Attack of Paroxysmal Auricular Tachycardia" *Heart* 1924 XI 67
- Cooke W T and White P D "Paroxysmal Ventricular Tachycardia" *Brit Heart J* 1943 V 33
- Dubbs A W and Parmet D H Ventricular Tachycardia Stopped on the Twenty first Day by Giving Quinidine Sulfate Intravenously *Am Heart J* 1942 XXIV 272
- Elliott A M and Fenn G K Long Continued Ventricular Tachycardia Report of an Unusual Case" *Am Heart J* 1934 IX 806
- Hepburn J and Rykert H E The Use of Quinidine Sulfate Intravenously in Ventricular Tachycardia *Am Heart J* 1937 XIV 670
- Howard T "Double Tachycardia Coexistent Auricular and Ventricular Tachycardia Due to Digitalis" *Am J M Sc* 1927 CLXXIII 165
- Mays A T Ventricular Tachycardia of Unusually Long Duration (77 Days) *Am Heart J* 1942 XXIII 119
- Palmer R S and White P D "Paroxysmal Ventricular Tachycardia with Rhythmic Alternation in Direction of the Ventricular Complexes" *Am Heart J* 1948 III 454
- Scott W "Observations on a Case of Ventricular Tachycardia with Retrograde Conduction" *Heart* 1921-1922 IX 297
- Stempien J and Katz K H "Quinidine and Potassium in the Treatment of Refractory Paroxysmal Ventricular Tachycardia" *Am Heart J* 1942 XXIV 555
- Strong G P and Levine S A The Irregularity of the Ventricular Rate in Paroxysmal Ventricular Tachycardia" *Heart* 1923 X 125

*Recent References (1944-1950)*

- Armbrust, C A Jr and Levine S A "Paroxysmal Ventricular Tachycardia A Study of 107 Cases" *Circulation* 1950 I 28
- Bell G O, Bradley R B and Hurxthal L M Paroxysmal Tachycardia Experiences

- with Massive Doses of Quinidine Intravenously in a Refractory Case *Circulation* 1950 I 939
- González Sabathie L On the Intravenous Use of Morphine in the Treatment of Paroxysmal Ventricular Tachycardia *Am Heart J* 1947 XXXIII 719
- Joseph S I and Rovenstine E A Cardiac Arrhythmias Prophylaxis and Therapy with Procaine Amide During Cyclopropane Anesthesia for Thoracic Surgery" *J Pharmacol & Exper Therap* 1951 CI 19
- Kayden H J et al "The Use of Procaine Amide in Cardiac Arrhythmias *Circulation* 1951 IV 13
- Mark L C Berlin I Kayden H J Rovenstine E A Steele J M and Brodie B B "The Action of Procaine Amide (N<sup>+</sup> (2-diethylaminoethyl) p aminobenzamide) on Ventricular Arrhythmias *J Pharmacol & Exper Therap* 1950 XCVIII 71
- Massachusetts General Hospital Case 74 from the Medical Grand Rounds "Ventricular Tachycardia *Am Pract* 1948 III 40
- Nathanson M H and Tober J "The Cardiovascular Effects of the Intranasal Administration of Mecholyl *Am Heart J* 1949 XXCVII 655
- Reich N E "Successful Use of a Massive Dose of Quinidine in a Case of Intractable Ventricular Tachycardia. *Am Heart J* 1944 XXVIII 256

---

## CHAPTER 33

---

# ATRIAL FIBRILLATION AND FLUTTER VENTRICULAR FIBRILLATION QUINIDINE THERAPY

---

Although it is quite possible that atrial fibrillation and flutter are as manifestations of abnormal physiology simply more advanced stages of the same process that gives rise to atrial paroxysmal tachycardia they are so different clinically from that disorder of rhythm that they demand an entirely separate chapter

Moreover although atrial fibrillation and atrial flutter are themselves very closely related in mechanism undoubtedly representing simply different stages or gradations of the same underlying process or disturbance of cardiac rhythm they do not however have the same clinical characteristics and they differ somewhat in treatment They will therefore be considered separately in this chapter Atrial fibrillation though apparently a more complicated mechanism than atrial flutter is far more common and clinically more important and so will be considered first

### ATRIAL FIBRILLATION

**Introduction** Atrial fibrillation is one of the commonest most interesting and most important disorders of cardiac rhythm it is fundamentally a disturbance of atrial origin and attended usually by absolute irregularity of ventricular action Its clinical existence suspected by Hering in 1903 and by Cushny and Edmunds in 1906 was proved in 1909 by Rothberger and Winterberg and by Lewis independently

Rothberger C J and Winterberg H Vorhofflimmern und Arrhythmia perpetua  
*Wien klin Wchnschr* June 17 1909 XXII 839

Rothberger and Winterberg were the first to publish satisfactory evidence that atrial fibrillation occurs in human patients their publication antedated by only a few months the independent demonstration by Lewis that atrial fibrillation is a common clinical condition I have selected and translated a few sentences from this work of Rothberger and Winterberg

Although the *pulsus irregularis perpetuus* has been known to clinicians for a long time it has only in recent years been described by Hering (1903) as a special form of cardiac arrhythmia characterized by particular features

The normal venous pulse curve shows with each heart beat three characteristic upstrokes the first of which precedes the apex impulse that is the pulse in the great arteries and represents atrial systole

In arrhythmia perpetua this wave which gives us evidence of activity of the right atrium is entirely missing and the phlebogram shows the characteristics of the so called positive or ventricular venous pulse

There has long been known in animal experimentation a very irregular heart rhythm namely atrial fibrillation (*Flimmern der Vorhöfe*) which is identical in all details with the signs of arrhythmia perpetua

Atrial fibrillation is accompanied by absolutely irregular ventricular action transmitted to the pulse this arrhythmia is of exactly the same character as that which we find in arrhythmia perpetua

In atrial fibrillation more or less delicate fibrillary movements occur which are of no significance for the movement of blood as a result in the phlebogram the pre-ventricular wave is missing and a positive venous pulse develops

The authors then describe electrocardiograms from experimental animals and from patients pointing to the three points of similarity between the records from animals with known atrial fibrillation and the records from patients with absolute arrhythmia (arrhythmia perpetua) These three points of resemblance are (1) absolute ventricular arrhythmia (2) absence of *P* waves and (3) presence of irregular oscillations of the galvanometer string due to the fibrillary waves themselves

Lewis Thomas Auricular Fibrillation a Common Clinical Condition *Brit M J*  
November 27 1909 II 1528

Lewis also published convincing evidence of the frequent clinical occurrence of atrial fibrillation

It is well known that in the late stages of mitral stenosis and in cases of general cardio-vascular degeneration the pulse is frequently continuously and extremely irregular The type of irregularity is remarkable in that in radial and cardiographic curves it defies analysis The nature of the arterial curves has given rise to the term *pulsus irregularis perpetuus* and it has been supposed that the rhythm of the heart producing it has its origin in the node of Tawara (hence the term nodal rhythm) The condition is extremely common

Facts are now at my disposal permitting of two conclusions

I That a rhythm arising in the neighbourhood of the node gives rise to a totally different clinical picture This conclusion is based upon a detailed examination (polygraphic and electrocardiographic) of a case of paroxysmal tachycardia in which it can be demonstrated that auricle and ventricle contract together This rhythm is a rare clinical phenomenon

II That the irregular pulse of mitral stenosis etc already referred to is due to fibrillation of the auricle

The second conclusion is based upon the following evidence

"1 The clinical irregularity presented by arterial and heart apex curves is unique The rhythm is entirely disorderly and the sizes of the beats do not correspond to the pauses which precede them Fibrillation of the auricle results in a

similar action of the ventricle and its action under these circumstances is unique experimentally

2 Electrocardiograms taken from patients exhibiting the irregularity show a number of irregular waves apart from the ventricular curve they are more clearly defined in diastole. They are found in no other disorder of the heart's action. They disappear when in a paroxysmal case the irregularity vanishes and are therefore due to a temporary and disorderly action of some part of the heart wall. Cardiographic curves give no evidence of such a disordered action in the ventricle. Fibrillation of the auricle yields curves which are identical in every respect and no such curves have been obtained by any other experimental means. Further the waves on the experimental electrocardiograms can be shown to correspond to the fibrillary movements in the auricle by means of synchronous tracings.

3 The venous curve in the clinical irregularity is of the ventricular type all the prominent waves occur during ventricular systole and there is no wave corresponding to a normal auricular contraction. The same statement applies to the venous curves in fibrillation of the auricle. The clinical and experimental curves are of the same nature.

**Incidence** Atrial fibrillation is common ranking probably third in frequency as a disturbance of rhythm premature beats and atrial paroxysmal tachycardia ranking first and second. Most statistics especially hospital figures indicate that atrial fibrillation is more common than paroxysmal tachycardia but this is almost certainly due to the fact that atrial fibrillation is a striking disorder usually permanent and easily recorded graphically while paroxysmal tachycardia is a transient disorder often overlooked or scarcely heeded and difficult to record graphically because of its short duration. Atrial fibrillation even of paroxysmal type rarely escapes notice and almost without exception comes eventually under medical scrutiny. In a group of 3 000 patients with cardiac symptoms or signs analyzed in New England (White and Jones 1928) 376 or 12.5 per cent were found to have atrial fibrillation 309 (82.2 per cent) of which were permanent and 67 (17.8 per cent) paroxysmal in type.

**Mechanism (abnormal physiology)** Absolute irregularity of the action of the heart termed in the past *delirium cordis* and absolute or perpetual arrhythmia was attributed at first to a variety of different mechanisms among them atrial paralysis with idioventricular rhythm, atrioventricular nodal rhythm controlling both atria and ventricles and the conflicting activity of multiple incoordinated abnormal atrial pacemakers. Then for many years it was widely believed that the condition is due to the establishment of a wave of excitation and contraction constantly circulating at a more or less irregular but very rapid rate about a more or less irregular and variable ring of muscle in the atria chiefly about the great veins giving off stimuli to the rest of the atrial muscle and to the ventricles the ventricles responding as rapidly as they can but at an irregular rate (Lewis 1921). This conception was based on fundamental observations of the circus movement of muscular contraction waves in experimental animals (Mayer 1908 Garrey 1912-1914 Mines 1914). It was shown that a contraction wave may continue to circulate around



a band of muscle if such a band is long enough to allow the point of origin of the wave to recover from its refractory (nonresponsive) stage by the time the circulating wave reaches it again and that such a circus wave can apparently be established in the dog's atrium by a rapid series of faradic stimulations. The circus wave has been thought to be the underlying mechanism of both atrial flutter its simplest manifestation and atrial fibrillation, its more complicated form. Recently however this theory of the circus movement has been challenged and another mechanism namely that of excessively rapid atrial discharge of stimuli from one atrial focus, proposed in its place (Scherf et al 1948 Prinzmetal et al 1949). The flutter waves have been clearly visualized by the use of slow motion pictures and have been seen to travel in all directions from an irritated focus and not in the form of a circus also it has not been stopped by a burn placed across a circus path (Prinzmetal et al 1949). Thus this new explanation of flutter and fibrillation of the atria relates them closely to the mechanism of ordinary paroxysmal tachycardia the difference being simply that of rate. However several difficulties remain to be explained including the rarity of atrial rates between those of flutter and of paroxysmal tachycardia the electrocardiographic differences and finally the clinical dissimilarities. More studies of this problem are obviously needed.

The rate of initiation of the excitation and contraction wave in the atrial muscular tissue in atrial fibrillation is very rapid averaging in man about 400 per minute and varying between 300 and 500. The speed is so great that areas of block or refractory points develop accounting for the irregularity of rate seen in the electrocardiogram as regards both atrial and ventricular action. Related to this same mechanism is that found in atrial flutter where the excitation occurs at a slower and much more regular rate (though not always absolutely regular) at 200 to 400 per minute averaging 300. Transitional stages between fibrillation and flutter are common at atrial rates of about 350 and they have been variously called 'impure flutter', 'flutter fibrillation' and 'coarse fibrillation' the last term referring to the coarse atrial deflections seen in the electrocardiogram a halfway stage between the wide regular oscillations of flutter and the fine irregular movements of fibrillation (Figure 158). A new term 'auricular tremulation' has been suggested for this intermediate stage (Pinchenzon 1937) but it seems unnecessary to multiply designations for the mechanism responsible for both 'atrial fibrillation' and 'atrial flutter'.

The ventricular response to the very abnormal atrial mechanism in atrial fibrillation is almost invariably grossly irregular and rapid when first encountered at about 130 to 150 per minute before therapy has been instituted and in the absence of organic or functional heart block. Heart block either permanent from disease or temporary from the functional effect of drugs reduces the ventricular rate but does not control the ventricular arrhythmia unless the block is rendered complete.

It is of interest to observe that in spite of the loss of sinoatrial control of

the heartbeat outside influences can still affect the heart (ventricular) rate when there is atrial fibrillation apparently through the action of the vagus and sympathetic nerves on the atrioventricular node and bundle thus excitement and exertion will increase the heart rate and changes in rate with respiration are often seen especially in sensitive nervous persons with neurocirculatory asthenia. In rare instances the ventricular rate may be controlled by ventricular

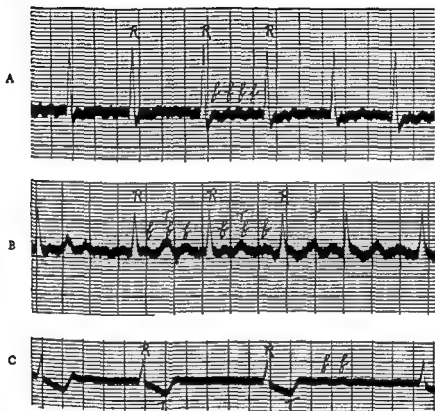


FIG 158 Electrocardiograms (Lead 2) showing atrial fibrillation (A) "Fine" type with high rate of atrial action (B) "coarse" type with slow rate of atrial action (C) atrial fibrillation with considerable degree of atrioventricular block (ventricular rate below 60) and inverted T waves (digitalis effect)

pacemakers in spite of the presence of atrial fibrillation. This happens in three conditions: (1) complete heart block, (2) ventricular paroxysmal tachycardia, and (3) ventricular escape or idioventricular rhythm superimposed on partial block. When for some reason, as from digitalis stimulation, the atrioventricular node becomes sufficiently irritable to control the ventricular action at regular rates of moderate speed, usually about 60 to 90 per minute. Ectopic contractions arising in the ventricle also often interrupt the arrhythmia induced by atrial fibrillation; this is most strikingly seen when every beat of supraventricular origin is followed by a premature beat to produce the

so-called bigeminal or coupled pulse characteristically found with digitalis intoxication. It is of interest to note that in such cases the ectopic or premature ventricular beats are always evenly spaced after the preceding beats of supraventricular origin even though the pairs occur irregularly. The explanation of this regular interval between the first and second beats of the couples in the bigeminal rhythm of atrial fibrillation is not certain, but it is probably due to re-entry of the normal beat at some point of local block or prolonged refractory period the muscle failing to respond at that point to the original stimulus but able finally to contract and to start a new heartbeat in adjacent muscle (which has recovered from its own refractory phase) when the original stimulus reaches it by a circuitous route.

The speed, length and points of block (or refractory state) of the flutter wave in the atria determine its existence as flutter or as fibrillation. Certain factors, particularly two drugs, influence these conditions.

*Digitalis* tends to cause intra atrial block by increasing the refractory period through its direct action on the atrial muscle, but its usual chief effect is to increase the rate and irregularity of the excitation wave and to shorten or hasten its course by decreasing the refractory period of the muscle through vagal action. This vagal action overrules the direct effect on the muscle. In this way digitalis acts to convert atrial flutter into atrial fibrillation, and sometimes this is followed by a return of normal rhythm. Digitalis, while increasing the atrial rate, practically always slows the ventricular rate in atrial fibrillation by increasing the grade of atrioventricular block, except in rare cases when massive doses may cause a regular idioventricular rhythm or ventricular paroxysmal tachycardia.

*Quinidine sulfate* slows the excitation wave (more effectively than quinine) by increasing the refractory period of the atrial muscle at the same time that it increases its duration. This increase in duration probably is necessary for the continuance of the atrial action which otherwise would always be quickly stopped (as it sometimes is) by the increase in the refractory period. The depressant and paralyzing action of quinidine on the vagus nerve acts to reinforce the direct effect of quinidine on the atrial muscle. The excitation wave takes a slower and more regular course under the effect of the quinidine. This drug has therefore a tendency to convert atrial fibrillation into atrial flutter. It also tends to increase the ventricular rate when the atrial rate falls. If the increase in the refractory period of atrial muscle under quinidine therapy is so great that it overbalances the longer duration of the excitation wave, the latter may be unable to continue and the abnormal mechanism abruptly ceases. When at such a time the sinoatrial or rarely the atrioventricular node resumes action, a regular heartbeat results, but if both of these nodes are themselves depressed by the drug, the heart may cease action altogether—a probable explanation of death that has occurred in a few cases under quinidine treatment when embolism was not responsible.

Thus the atrial rate may be increased in rate by digitalis from under 300 per minute to over 500, while the reverse is the effect from quinidine. Even

though the usual experimental data and theoretical considerations indicate that digitalis and quinidine may act in opposite ways on the refractory period of the atrial muscle and thereby cause opposed effects clinical experience has shown that often it is worthwhile to digitalize before administering quinidine partly because normal rhythm is more readily restored thereby and partly because the ventricular rate is kept from rising too high when the rate of the atrial contractions is reduced by the quinidine. It is also possible that fixed atrial flutter may be prevented by preliminary digitalization although of that there is as yet no proof.

Finally it should be stated that atrial fibrillation is by no means a constant or perpetual condition as was at one time thought. It is frequently paroxysmal in nature although once established for a period of several weeks it does tend to persist.

**Etiology Cause** The cause of the establishment of the abnormal mechanism of atrial fibrillation is often obscure. In most cases there is an important grade or type of heart disease or an important toxic or disease process of other nature but sometimes there is no such cause the individual seeming perfectly healthy without heart disease or poisoning of any sort. Thus the condition is fundamentally a functional disorder and not in itself to be classed as heart disease.

Atrial fibrillation is attended usually by little or no myocardial degeneration or inflammation but nearly always an unusual degree of strain or nervous excitability exists. Mitral stenosis and thyrotoxic heart strain are the two cardiac conditions relatively most often associated with atrial fibrillation hypertension and coronary heart disease are only occasionally complicated by this arrhythmia. Aortic valve disease congenital defects syphilitic aortitis and bacterial endocarditis are uncommonly associated with atrial fibrillation probably because the atrial strain and nervous stimulation are less. The mystery of the rarity of atrial fibrillation in subacute bacterial endocarditis may be explained by the fact that this infection only infrequently attacks mitral valves that are badly stenosed and that it selects rather the aortic valve and slightly deformed mitral valves from which defects there is little or no atrial strain. Atrial fibrillation is more common when the left atrium is under strain or enlarged no matter what the cause of the enlargement than when it is of normal size the commonest causes of such strain and enlargement are mitral valve deformity (especially stenosis) and failure of the left ventricle due to hypertension myocardial infarction or advanced aortic valve disease.

Once upon a time it was customary to label any individual over the age of fifty years who showed atrial fibrillation and nothing else wrong as an arteriosclerotic (meaning coronary) cardiac victim but now it is realized that such designation is unjustified. It is perfectly true that cardiac arrhythmias like gray hairs are more common with increasing years and that a less adequate coronary circulation may be somewhat responsible but by and large even in older persons it is wiser in the absence of other evidence to regard atrial fibrillation as a disorder of function rather than as a sign of heart disease.

Noncardiac etiologic factors responsible occasionally for atrial fibrillation either in paroxysms or in established form are poisoning by toxic agents of all sorts such as excessive use of tobacco and alcohol especially in unaccustomed amounts or an occasional spree gas poisoning food poisoning and infectious diseases (like pneumonia). Sometimes violent exertion and excitement, trauma and surgical operations (especially of the thorax) are responsible for the onset of paroxysmal or permanent atrial fibrillation with little or no heart disease. In a group of 49 cases of atrial fibrillation without heart disease reported by Orgain Wolff and White (1936) the exciting factors responsible for the onset of atrial fibrillation (paroxysmal or permanent) were apparently pneumonia malarial chill pelvic abscess burns surgical operation ether alcohol gallbladder colic vomiting exertion, and emotion (excitement and fear).

Finally there appears to be some sort of susceptibility or nervous hypersensitiveness that predisposes to this abnormal mechanism. Several members of one family may be affected even in youth, without serious disease and in fact in some cases without any evident disease at all.

In an analysis of 575 consecutive cases of atrial fibrillation reported by McEachern and Baker (1932) the chief etiologic relationships were as follows: rheumatic heart disease 34.4 per cent, coronary disease and old age 31.1 per cent, hypertension 16.9 per cent, thyrotoxicosis 7.5 per cent, emphysema 5.0 per cent, syphilis 3.0 per cent, and miscellaneous 2.1 per cent. In the series of 376 cases of atrial fibrillation reported by White and Jones (1928) 346 patients had definite evidence of organic heart disease while 30 (8 per cent) were apparently free from heart disease. Almost half 158 (45.6 per cent) of the organic group of 346 cases belonged to the rheumatic type with or without complications. Seventy-four (21.4 per cent) of the cases had coronary heart disease without other complications, 15 (4.3 per cent) had hypertension alone while 92 others (26.6 per cent) had hypertension complicating other conditions and 14 (4.1 per cent) had thyrotoxicosis alone.

**Sex.** The sexes are unequally affected by atrial fibrillation, paroxysmal and permanent. It was stated in the second edition of this book that about twice as many males as females show this arrhythmia, perhaps because men are generally subject to greater strain than are women. A more recent review of 10,000 cases which included 645 patients (6.45 per cent) with atrial fibrillation, electrocardiographed at the Massachusetts General Hospital from January 3, 1939 to February 6, 1942, showed a ratio of 71 per cent males (455 cases) to 29 per cent females (190 cases).

**Age.** Atrial fibrillation is very rare in infancy and early childhood, uncommon in adolescence but increasingly more frequent in each decade of life. It is generally true in the case of all other disorders of heart rhythm. Of the 575 cases of atrial fibrillation reported by McEachern and Baker (1932) 0.5 per cent were under ten years of age, 4.2 per cent ten to twenty years old, 5.4 per cent twenty to thirty, 15.0 per cent thirty to forty, 20.2 per cent forty to fifty, 26.1 per cent fifty to sixty, 20.5 per cent sixty to seventy, 7.8 per

cent seventy to eighty and 0.3 per cent eighty to ninety. Despite the falling off in the figures of absolute incidence in the last three decades of life atrial fibrillation actually continues to increase in frequency relative to the rapidly decreasing number of persons surviving to advanced age.

**Pathology.** There is no pathologic change characteristic of atrial fibrillation. There may or may not be organic heart disease; usually there is. There may or may not be myocardial abnormality other than hypertrophy; usually there is not. Extensive heart disease, myocarditis and myocardial degeneration may exist without atrial fibrillation. The atria are usually enlarged (dilated) in atrial fibrillation and their walls may show areas of degeneration and fibrosis which however are neither uniform nor specific.

**Symptoms.** Atrial fibrillation, especially if it is of permanent nature and properly treated, may exist without any symptoms. Usually however the patient is aware of the irregular heart action which he describes variously as fluttering, irregular palpitation or pounding, skipping or tumultuous action. Thus consciousness of the abnormal heart action is particularly marked during paroxysms of atrial fibrillation and at the time of the onset of permanent atrial fibrillation before the ventricular rate has been controlled. At such times the distress, nervous irritation and fear or worry may be so great that the patient feels and may even be thought to be far sicker than he is. He may be greatly distracted with the thought of impending death and a feeling that his heart must burst or stop after its vigorous leaping about. Even after full reassurance much discomfort usually persists and although the fear is gone complete or partial invalidism may come with every paroxysm of atrial fibrillation or may persist if the paroxysms occur frequently or if the arrhythmia becomes permanent. Gradually after the patient becomes accustomed to the recurrent paroxysms or to the constant arrhythmia, especially if the ventricular rate is controlled by treatment, the symptoms decrease and as a rule finally disappear entirely.

Palpitation is the characteristic symptom of atrial fibrillation. Dyspnea and pain are much less common but they may develop as a part of neurocirculatory asthenia if there is an associated marked psychic element (from fear and nervous exhaustion). Dyspnea may set in if myocardial fatigue or pulmonary engorgement due to mitral stenosis develops as the result of the rapid irregular heart action or the distress of an angina pectoris may appear due to extra work imposed by rapid heart action on a myocardium very badly supplied with blood. Other symptoms of the frequent complication of congestive failure are occasionally seen. The rarity of the association of atrial fibrillation with angina pectoris is an interesting problem best explained by the limitation of activity that occurs with atrial fibrillation because of palpitation, dyspnea, fear or medical advice, there being no longer enough strain on the myocardium to exceed the reserve of the limited coronary circulation. When the heart action is very rapid in atrial fibrillation there may be weakness, dizziness and faintness due in part at least to cerebral anemia. As in the case of paroxysmal tachycardia, syncope may rarely occur at the end of a paroxysm.

of atrial fibrillation due to failure of the normal pacemakers of the heart to resume action at once

**Signs** The characteristic sign of atrial fibrillation is absolute irregularity of the beating of the heart whether the rate is rapid or slow. Although this sign is not absolute proof of atrial fibrillation there are very few exceptions (cross sinus arrhythmia multiple premature beats and atrial flutter with varying grades of heart block). Graphic records are useful in confirming the diagnosis of atrial fibrillation but they are usually unnecessary so far as this one particular finding is concerned a phlebogram will show atrial fibrillation but an electrocardiogram is of more value since it gives other additional information for example the effect of digitalis on the T waves (Figures 152 page 832 and 158C page 897) and the state of the coronary circulation

Often when the patient is first seen before treatment is started the heart action may be so rapid irregular and weak that some beats fail to cause pulsation in the peripheral arteries, as a result the apex rate is faster than the radial pulse rate and the difference is called the pulse deficit. When the ventricular rate slows as the result of rest and digitalis the heart action becomes steadier stronger and more regular fewer beats or none fail to reach the wrist until finally with a slow heart rate the pulse deficit entirely disappears although of course the atrial fibrillation itself persists. The apex rate at first may be as high as 150 per minute and the radial pulse rate as low as 100 with a pulse deficit of 50 later after full digitalization both apex and radial rates may be 75 with no pulse deficit at all the radial rate sometimes actually rises with improved strength of pulse as the heart rate slows. Generally at the onset the radial pulse rate is high as well as the apex rate and both drop with treatment (Figure 151 page 829). Although with training in palpating the pulse less deficit is found in cases of atrial fibrillation with rapid ventricular rate than before such training nevertheless there often is an appreciable deficit at fast rates and to chart carefully several times a day the amount of pulse deficit along with the apex rate is one of the best ways to follow the effects of treatment. The observer usually a nurse must be taught in such cases to record not only the radial pulse rate but what is much more important the apex heart rate also. This procedure used to be neglected at times even in good hospital clinics or in private practice and as a result there used to be considerable uncertainty about the course of the true heart rate of these cases but in recent years this difficulty has been largely eliminated.

There may be no other signs of the abnormal atrial mechanism than the absolute irregularity of the heartbeat and the electrocardiographic evidence. Usually however there is some cardiac enlargement due to the presence of some sort of heart disease this may be great or little or primarily of left ventricle of right ventricle or of the atria (especially of the left atrium in mitral stenosis). Murmurs may or may not be found if present they are due most commonly to mitral stenosis or to cardiac dilatation. There may be signs of congestive heart failure or of constrictive pericarditis.

The blood pressure may be normal low or high with atrial fibrillation

Often hyperpiesia is present and this important condition may be missed if the blood pressure is not measured. Because of the difficulty of obtaining accurate figures of blood pressure in the presence of atrial fibrillation especially with rapid ventricular rate due to the greatly varying force of successive beats sphygmomanometry was at one time largely abandoned in cases of atrial fibrillation or made very complicated by the use of special technic such as taking the digital pressure and comparing it with the usual brachial standards or calculating the average brachial pressure by a fractional method. As a matter of fact clinical experience in hundreds of cases has shown the feasibility and relative reliability of taking the blood pressure in the routine way in cases with atrial fibrillation. Although there is more or less variation in pressure of beats a sufficiently accurate average can be quickly determined in a rough manner for both systolic and diastolic pressures. These pressure readings usually correspond quite closely to those of the same cases during normal heart rhythm either before or after the atrial fibrillation. Moreover when the ventricular rate is slowed by digitalis the beats become much more uniform in force and may vary very little or not at all on blood pressure estimation therefore if one is in doubt about the pressure in a difficult case sphygmomanometry can easily be repeated after the heart rate has been slowed or normal rhythm restored. Weak beats have a smaller pulse pressure with lower systolic and higher diastolic levels.

Roentgen ray study is not usually of much help although it is always essential to make such a study an integral part of a thorough examination of every patient with cardiac symptoms or signs. The ventricular arrhythmia is often evident fluoroscopically but it is less easily analyzed by roentgen ray than by auscultation or electrocardiography. The abnormal atrial mechanism is generally indistinguishable by roentgen ray the atria appearing to partake only of the ventricular movement. Abnormalities of cardiac size and shape if pronounced are of course easily made out roentgenologically and may help with the finding of atrial fibrillation to establish such a diagnosis as mitral stenosis.

Electrocardiography is of the greatest assistance in confirming the diagnosis of atrial fibrillation although this confirmation is often unnecessary. Electrocardiography is still more useful in showing the presence or absence of associated abnormalities like bundle branch block and in following the effect of digitalis therapy on the T wave or of quinidine treatment on the atrial mechanism. The oscillations caused by the excitation wave in atrial fibrillation are usually best made out in Lead 2 but sometimes they are maximal in Lead 3. Precordial leads over the ventricles are usually disappointing but if the exploring electrode is placed over the right atrium just to the right of the sternum in the position of the first of the six routine precordial leads that is in the fourth intercostal space or better still in the third intercostal space just at the right of the sternum the site of the so called special atrial lead point (or over the left atrium esophageally) the f or fibrillation waves may be very evident.

**Course and prognosis.** Atrial fibrillation may be of trivial importance or it may be very serious. If it occurs in the form of transient paroxysms in a person



without heart disease it may be disagreeable but nothing more recurrent and on at longer or shorter intervals or perhaps only once or twice without recurrence. Untreated paroxysms of atrial fibrillation usually last a few hours, with ordinary limits of a few minutes to several days and very rarely extreme limits of a few weeks or months or even years (Fogel 1943). Even if it occurs in permanent form atrial fibrillation may cause little or no disability if there is no important heart disease and if the heart rate is kept reasonably slow by constant digitalis therapy or controlled by organic heart block without drugs. Cases have been known with a history of paroxysmal or of permanent atrial fibrillation over periods of many years even thirty or more. Paroxysms may occur only once or twice and be followed by long intervals of freedom for many years or they may recur frequently at intervals of months or weeks and yet not cause disability or more than passing discomfort if the heart is strong.

In general atrial fibrillation like premature beats and paroxysmal tachycardia is a functional disorder that in itself is a far less serious factor in crippling or in shortening life than is the underlying heart disease or other condition that may be present provided that either the atrial fibrillation is transient or the ventricular rate is controlled by treatment. Now that quinidine therapy is successful in restoring normal rhythm in a good many cases of permanent atrial fibrillation this type of atrial fibrillation can sometimes be transformed into that of paroxysmal nature with long intervals of months or even many years of freedom from any disturbing cardiac arrhythmia. Long lives of full activity may thus be carried on through the proper use of quinidine and digitalis in spite of the occasional occurrence of temporary disturbing paroxysms of atrial fibrillation or of the presence of permanent atrial fibrillation.

**Complications.** Unfortunately atrial fibrillation cannot always be regarded in so optimistic a way as that expressed above. Since it so often complicates very serious heart disease its occurrence may precipitate heart failure and even death unless successful therapy is quickly instituted. It is always somewhat of a burden even to a normal heart though in such cases the cardiac reserve is sufficient to take care of the disorder. The tachycardia rather than the arrhythmia is the serious factor and if that is reduced to a normal heart rate the circulation may be maintained in a satisfactory way in spite of the irregularity. The fact however that the circulation is more efficient with normal rhythm than with atrial fibrillation at the same heart rate makes it often worthwhile to attempt the restoration of normal rhythm for there may come a time in an individual case when the more economic circulation maintained by normal rhythm means the difference between cardiac sufficiency and cardiac failure. Although long-continued uncontrolled atrial fibrillation alone may in rare cases cause a normal heart muscle to fail the ordinary case of heart failure caused by atrial fibrillation is one showing extensive heart disease especially mitral stenosis. Proper treatment by digitalis and rest may prolong life for a number of years probably sometimes for as many as ten or twelve but finally there comes a time often at about forty five to fifty years of age when

with advanced mitral stenosis the heart reserve can no longer be maintained and death comes in spite of the best treatment. The early recognition and early and persistent treatment of the atrial fibrillation which appears as a complication of heart disease is of great importance in prolonging life and reducing disability in cardiac cripples.

There is one condition, thyrotoxicosis, in which atrial fibrillation either in paroxysmal or permanent form is especially likely to be the earliest sign of cardiac strain. If the thyrotoxicosis is not corrected the atrial fibrillation may become established and even eventually cause heart failure and death because the ventricular rate is difficult to control until the thyrotoxicosis itself is controlled. It is important always to consider the possible existence of thyrotoxicosis in any case of atrial fibrillation of unknown cause that is with out sufficient pathologic change in the heart to account for it particularly if it is difficult to control the ventricular rate with digitalis.

An important complication of atrial fibrillation besides heart failure is embolism into cerebral, renal, splenic or peripheral arteries causing hemiplegia of varying degrees and duration and other evidences of infarction, the embolus coming from an intracardiac thrombus usually in the left atrium. The stagnation of blood in the atria when they have ceased coordinate contraction favors the development of thrombi especially in the appendages. Pieces of these thrombi may break off and be precipitated into the blood stream more commonly in the systemic circulation less commonly in the pulmonary circulation, the emboli getting loose either during the fibrillation or at the time of the return to normal rhythm which occurs either spontaneously or as the result of quinidine therapy. The complication of embolism in atrial fibrillation is infrequent but often serious and sometimes fatal.

In very rare cases of mitral stenosis and atrial fibrillation there is formed free in the left atrial cavity a large spherical or ball thrombus which when it does occur partly occludes the atrioventricular ostium and may even temporarily obstruct it to cause collapse of the patient. A unique case with ball thrombus in the right atrium has been discovered (Wright et al 1944).

Sudden death is rare in atrial fibrillation its cause is not known although the onset of ventricular fibrillation has been suggested as responsible.

**Treatment.** The treatment of atrial fibrillation includes A that of the condition itself and of its complications and B therapy directed to prevent paroxysms of absolute arrhythmia or recurrence of the atrial fibrillation if once abolished.

**A. The direct therapy of atrial fibrillation** varies somewhat with the condition of the individual patient.

1 **Rest and digitalis.** If there is congestive failure or very serious heart disease quinidine should only very rarely be used. Absolute rest should be enforced and full digitalization carried out as rapidly as necessary. For an adult with atrial fibrillation who has not received digitalis or strophanthine and for whom emergency treatment is not needed digitalis leaf in 0.1 gm (1½ gr) pills may be given at the rate of one pill three times a day for 4 or 5 days or

0.06 gm (1 gr) three times a day for one week such a course to be followed by a ration of one pill daily of either dosage depending on the individual case constantly thereafter so long as the fibrillation persists. This therapy should suffice to reduce the heart rate to normal by causing heart block and to keep it normal this dosage is an average amount and may have to be decreased or increased in individual cases. For emergency therapy 0.4 gm (6 gr) of standardized digitalis in solution (e.g. Digifolin) may be given intravenously to be repeated in four hours and again in the same or smaller amount in eight more hours if necessary or Cedilanid 4 cc (0.8 mg) may be given by vein to be repeated in four hours or digitoxin 0.6 mg may be administered by mouth or vein and repeated in four hours or strophanthin (ouabain) 0.25 to 0.5 mg (1/240 to 1/120 gr) may be injected intravenously to be repeated in twelve hours if needed these measures should be followed by a daily ration of one 0.1 gm (1½ gr) or 0.06 gm (1 gr) digitalis leaf pill. For further details of digitalis therapy see Chapter 30.

2 *Quinidine therapy* A striking discovery concerned with the control of the functional atrial disturbance in fibrillation and flutter has been the therapeutic application of quinine and its isomer quinidine. The effective use of quinine in the control of rebellious palpitation was first mentioned by Senac in 1749 and rediscovered a century and a half later by a patient of Wenckebach (1914) another alkaloid of the cinchona bark quinidine an isomer of quinine was found by Frey to be much more effective than quinine (1918). Although substitutes for commercial quinidine have been tried (see below) nothing more effective has been found as yet.

If the patient with atrial fibrillation has had no congestive failure or serious heart disease or history of embolism he should be considered a possible candidate for quinidine therapy. At least two thirds of all such patients can be restored to normal rhythm by this treatment and half of these somewhat more than one third of the original total number can maintain normal rhythm for at least several months sufficiently long to be considered definitely benefited by the therapy. Some cases maintain normal rhythm for years even for ten years or more in a few cases with relief of symptoms and a return to normal active lives. One of my patients has maintained normal rhythm for twenty five years having been one of the very first cases of persistent atrial fibrillation to whom I gave quinidine soon after its introduction to this country. Successful quinidine treatment has been an important accomplishment in medical progress.

The percentages of successful restoration of normal rhythm in series of patients reported in the literature vary widely from 7 to 94 per cent averaging about 60 per cent. This wide variation is due in part at least to selection of cases and in part to dosage and other factors. Two relatively recent reports give figures of 23 out of 34 cases (68 per cent) maintained for over three months in 16 (Laake, 1945) and 44 out of 50 cases (88 per cent) maintained in 20 for more than a month (McMillan and Welfare 1947). The more normal the heart fundamentally the more likely is quinidine to act

successfully and safely. Hence it is particularly indicated when the arrhythmia is simply a very annoying disorder of function. There are however cases who are dangerously ill in whom the drug can be lifesaving as for example (1) in restoring normal rhythm in a patient with congestive heart failure maintained by the tachycardia of his atrial fibrillation which is resistant to digitalis control the heart rate being lower during normal rhythm in such cases than during atrial fibrillation and (2) in reducing the likelihood of the deposition of further intra atrial thrombi which might become emboli in patients with atrial fibrillation who have already suffered from embolism contrary to the classical rules of quinidine therapy (White and Blumgart 1942).

The patient receiving quinidine in large dosage to restore normal rhythm should be under close observation preferably in bed and where electrocardiographic observations can be made so that the effect of the drug can be accurately followed and its toxic as well as its beneficial action noted. Since quinidine in large dosage is a poison it must be used with care and by the exercise of care accidents and fatalities that have been reported in rare cases in the past can largely be avoided. A good method of administration of quinidine that has been found effective is to give it by mouth in the form of the sulfate in tablets or powders of 0.2 gm (3 gr) each. A test dose of a single tablet or powder may first be given to make sure that the individual is not unduly sensitive such sensitiveness is however very rare. If no toxic symptoms (of cinchonism—see below) appear administration of the drug in large dosage can be begun. Of various schedules of dosage two are as follows: (a) 0.4 gm (6 gr) that is two tablets or powders every two hours for five doses for example at 10 A.M., 12 M. and 2, 4 and 6 P.M. making a total of 2.0 gm (30 gr) in the day continuing this regime for two or three days at a time if normal rhythm is not restored during the first day or on the following night but stopping the drug on the appearance of toxic symptoms. Normal rhythm or obstinate atrial flutter (of more than three days duration) in a few cases 6 or 7 or 8 doses of 0.4 gm (6 gr) each at two hour intervals in a day have succeeded when the five doses have not. (b) 0.4 gm (6 gr) every four hours day and night except for the omission of one night dose during sleep, for a few days if necessary—the daily dose by this procedure will also equal 2.0 gm (30 gr) but this method is less reliable. Sometimes smaller doses down to one half the amount noted above or larger doses up to several times the above mentioned amount (even 6.0 gm [100 gr] or more a day) have been given or recommended but it is probable that the methods outlined here are as satisfactory as any and better than most. Massive doses of more than 4 gm (60 gr) of quinidine sulfate in a day are in general inadvisable and dangerous in the treatment of atrial fibrillation but when life is in jeopardy after prolonged ventricular paroxysmal tachycardia it is fair to take the risk of the larger doses (see Chapter 32).

In special emergencies or when the drug cannot be taken by mouth quinidine can be given intramuscularly or intravenously preferably the former because of the danger of toxic effects from rapid administration by vein. It

can be given in the form of a solution of either the lactate the gluconate or the hydrochloride ( injectable ) in the dosage of 0.2 to 0.5 gm (3 to 7½ gr) and repeated at two hour intervals as needed and as tolerated. On occasion, quinine dihydrochloride 0.5 gm (7½ gr) intramuscularly at two hour intervals has proved effective but in general for the treatment of cardiac arrhythmias quinine is inferior to quinidine.

So soon as toxic symptoms (cinchonism) of any important degree develop—marked tinnitus deafness, urticaria nausea vomiting diarrhea intraventricular block (ascertained by electrocardiogram), and very rapid regular heart action—the drug should be discontinued. Observation of the patient should always be made for toxic drug effects before the administration of each new dose and electrocardiograms should be taken several times during the day routinely at least after every other dose or even oftener. An increase in ventricular rate is natural during quinidine therapy although it is not always encountered when the atrial rate falls, atrioventricular conduction improves so that the ventricular rate rises and atrial and ventricular rates tend to approach a common level therefore even if a tachycardia develops it need cause no concern if it does not exceed 130 or 140 if it rises higher the drug should be discontinued for either the tachycardia may produce a very disagreeable palpitation or it may mean that there has developed a dangerous toxic heart rhythm such as ventricular paroxysmal tachycardia. An unusual toxic manifestation of the oral use of quinidine sulfate—high fever—has been reported (Sturnick 1942).

If normal rhythm appears the large doses of the drug should be reduced to daily rations for a shorter or longer interval as desired for example one 0.2 gm (3 gr) tablet three or four times a day for a few weeks or the quinidine sulfate may at once be discontinued altogether. If however the drug is continued every day for many months it tends eventually to lose its effect or it may cause annoying tinnitus deafness or looseness of the bowels so that occasional periods are to be recommended in which the drug is withheld altogether for a few days or a few weeks if possible. Much judgment is necessary in dealing with an individual case and experience with that case must control the therapy. In fact the patients themselves often become expert in handling the situation and are then better able to arrange time and amount of doses of quinidine than are their physicians. For example patients may find that they do not need the drug except at certain times during or just before some particular effort against which they require special protection for their heart for a few hours or a few days. In such instances the quinidine should be taken by mouth about 1½ hours before the particular strain that tends to cause the atrial fibrillation. The effect of a dose of quinidine sulfate given by mouth reaches its height in 1 to 2 hours and ceases in 4 to 5 hours.

If persistent atrial flutter appears it is best to stop the quinidine and to resort to digitalization to attempt to control this difficult disturbance of rhythm. Atrial flutter is a natural transitional stage in the change from atrial fibrillation

to normal rhythm but it is usually brief and often too transient to be recorded electrocardiographically

Serious accidents can happen during quinidine therapy but they are very rare and in carefully selected cases very unlikely. They include embolism due to pumping out by the heart of bits of intracardiac thrombus on restoration of normal atrial action. Embolism can however occur with persistent atrial fibrillation alone and in fact does so then as often as upon the return of the heart to normal rhythm. Sudden death without embolism has also been noted in several cases during quinidine therapy and the cause has been variously explained by respiratory paralysis, cardiac paralysis, ventricular fibrillation or other mechanism. Cardiac standstill is the most likely explanation being due to the paralysis of both pacemakers of the heart in the sinoatrial and atrioventricular nodes as the result of the toxic effect of the quinidine when these nodes are depressed and the abnormal mechanism of atrial fibrillation is brought to an end by the drug there may be no available pacemaker to take up the function of exciting the heartbeat death resulting. The finding of atrial standstill in two cases in which atrial fibrillation was abolished by quinidine has been noted by Wolff and White (1929) fortunately in these cases the atrioventricular node excited regular ventricular beats until the atria recovered their activity.

Digitalis may or may not be used with the quinidine in the attempt to abolish atrial fibrillation. It seems to be helpful and is generally to be recommended though it is not always necessary. It may be used in the dosage of 0.06 gm (1 gr) of digitalis leaf or 0.1 mg of digitoxin three or four times a day for five to seven days.

If normal rhythm is not restored by quinidine sulfate in the course of two or three days the drug should be discontinued and full digitalization should then be established and maintained if it has not already been accomplished. After a short interval of one to several weeks a second course of quinidine sulfate just like the first may be administered if desired and if that too is unsuccessful even a third course may be given later after another interval perhaps of a few months and with some variation of dosage. If digitalis is not used with the quinidine during an unsuccessful course it may be tried with the next course. It is of interest and importance to note that occasionally a second or third course or a larger dosage of quinidine sulfate has proved successful after early attempts have failed.

In successful quinidine therapy normal rhythm is generally restored after a few doses on the first or second day of a course of the drug. Infrequently atrial fibrillation may be banished by the single test dose or after the first regular dose of the course. Normal rhythm usually persists after its restoration for at least several weeks or months and sometimes for years. If atrial fibrillation recurs it should be treated again in the same way as at first but if it recurs often and normal rhythm lasts repeatedly for only a few hours, days or weeks it is best to abandon further quinidine therapy and to establish and

maintain digitalization. In such cases digitalization usually supports a satisfactory circulation and keeps the patient in a good enough state of health without the bother of frequent courses of quinidine and the annoyance of frequent shifting of the heart beat from normal rhythm to atrial fibrillation and back again. However, not infrequently digitalis and quinidine are helpfully given together: the former to help to maintain an improved myocardial tone and to prevent much tachycardia when atrial fibrillation occurs, and the latter to reduce the frequency of paroxysms of atrial fibrillation or to prevent them altogether.

3 *Other measures of treatment of atrial fibrillation* are of less importance than the use of digitalis and quinidine; nevertheless some measures are useful and often necessary. Avoidance of unnecessary physical and mental strain, fatigue, infections, overeating, and intemperate use of tobacco, tea, coffee, and alcohol (small amounts of these are often permissible) should always be a matter of routine, even though the atrial fibrillation is the only abnormality. The more trouble of other sort there is, especially in the form of heart disease and failure, the greater naturally must be the limitation imposed on the patient. Exercise, if possible, should be encouraged in mild form, especially walking, but it is to be remembered that although the heart rhythm no longer originates in the sinoatrial node, the heart rate is still subject to outside influences, apparently through nerve action on atrioventricular conduction. Excitement and exertion will increase the heart rate in spite of digitalis, even more than is the case in normal rhythm.

Special restrictions and special diets for atrial fibrillation are unnecessary. Other drugs than quinidine and digitalis are also, as a rule, unnecessary. Synthetic quinidine and dihydroquinidine are effective but not superior to commercial quinidine, while quinine is much less effective (Alexander et al 1947). Strophanthus squill, apocynum, and convallaria may be effective in the manner of digitalis, but they are inferior members of the digitalis group, except in the case of strophanthin or ouabain, which is more potent than is necessary and may be actually dangerous if given in large or often repeated doses—its use is much better limited to emergency treatment of congestive failure.

In recent years two other drugs have been introduced as substitutes for quinidine in trying to abolish atrial fibrillation: fagarine from South America (Deulofeu et al 1945; Taquini 1947; Scherf et al 1949) and atabrine (Gertler and Yohalem 1949). Both have been effective to some degree but need further study. Incidentally fagarine can cause serious ventricular irritation.

Symptomatic treatment and the therapy of complications or of other conditions associated with atrial fibrillation should be carried out with little or no regard to the arrhythmia.

Surgical operations and anesthesia should not be withheld when they are obviously necessary procedures; the atrial fibrillation is not a contraindication to their execution, although it is always wise to control the heart rate or the

arrhythmia first by the use of digitalis or quinidine. It is essential to remember that thyrotoxicosis is an important cause of atrial fibrillation and that it may be difficult or impossible to control this arrhythmia until the thyrotoxicosis itself is corrected either surgically or medically. It has been also of much interest with thyrotoxicosis present to observe the calming influence on the heart rate either in normal rhythm or in atrial fibrillation of the administration of iodine for a short time in preparation for operation (for example 5 gr of potassium iodide or 5 drops of Lugol's solution three times a day for a week). The discovery of this effect was made accidentally by Trousseau many years ago (1863) when he gave by mistake a prescription for tincture of iodine instead of tincture of digitalis to a patient with thyrotoxicosis and tachycardia. The heart rate was reduced much more readily by the iodine than by the digitalis which was later substituted on discovery of the original error.

For the discomfort due to the palpitation induced by atrial fibrillation either in paroxysmal or in permanent form various medicines may be helpful in particular bromides (for example 1 gm [15 gr] of the triple bromides in solution two or three times a day for a few days as needed). Codeine and morphine should rarely be employed and then only to tide over some exceptionally severe period of palpitation and associated discomfort or pain especially when the tachycardia produces pulmonary edema or the status anginosus before digitalis or quinidine becomes effective. Since paroxysmal atrial fibrillation is commonly recurrent there is a real danger of habit formation (morphinism) in the use of the opiates.

**B** Therapy directed to prevent paroxysms of atrial fibrillation or recurrence of "permanent" arrhythmia is much like that already outlined for the prevention of paroxysms of tachycardia in Chapter 32. In the first place factors that irritate the heart or nervous system and favor the onset of atrial fibrillation should be prevented or at least reduced to a minimum such factors include nervous excitement and fatigue, sudden violent effort, prolonged exhausting exertion, hearty meals, excess of tobacco, alcohol, tea or coffee, worry and late hours. Secondly there may be conditions of ill health which favor the appearance or persistence of atrial fibrillation such as focal infections, general diseases, local strain of muscles or joints, painful conditions like stones in kidney or gallbladder and heart failure. These conditions should be corrected so far as possible but not too abruptly or vigorously. Thirdly there is more or less specific therapy possible by the administration of quinidine sulfate in daily rations of 0.2 to 0.4 gm (3 to 6 gr) once, twice, three or four times a day according to need, constantly for a few doses or for days at a time. Often such quinidine therapy is successful at least in reducing the number and duration of the paroxysms of atrial fibrillation even if not in completely preventing them. It is a common experience that patients who have numerous long paroxysms each lasting twelve to twenty-four hours or more and coming as often as once or twice a week find that the attacks become infrequent and short under quinidine therapy lasting but two or three hours each time and coming perhaps once or twice a month. Finally when quinidine sulfate rations



are ineffective it is wise to try the effect of digitalization and its maintenance. In rare cases digitalis seems to reduce the number and duration of the paroxysms but its chief advantages lie in the facts (1) that when atrial fibrillation does occur depression of atrioventricular conduction already exists as the result of the digitalis effect and so the ventricular rate rises less than without digitalization and (2) that digitalis tends to maintain atrial fibrillation as a permanent disorder of rhythm after it has recurred paroxysmally and so with its simultaneous control of the ventricular rate permits a much pleasanter existence than when atrial fibrillation is constantly coming and going. Sometimes quinidine and digitalis may be combined successfully in preventive therapy but if in spite of these drugs there is much discomfort from recurrent attacks of atrial fibrillation other medicines especially the bromides or phenobarbital may prove useful in reducing the distress. The bromides should be used cautiously to avoid a toxic effect.

Protection of the heart from disturbing arrhythmias during surgical operations on and about the heart has been accomplished by the preoperative use of quinidine sulfate and the administration of procaine to the exposed heart or by intrapericardial injection but the degree of effectiveness of these procedures has not yet been fully determined. In lung surgery too quinidine given preoperatively may prevent arrhythmias.

Reassurance so far as the atrial fibrillation is concerned is almost always an important part of the therapy but the significance of the condition must not be minimized to the extent that the patient neglects necessary treatment.

**Differential diagnosis** Atrial fibrillation has to be differentiated from gross sinus arrhythmia, multiple premature beats, paroxysmal tachycardia and atrial flutter. The most important point in differentiation of atrial fibrillation from any of these other disturbances of rhythm is the absolute irregularity of its rhythm which is almost invariably present and rarely simulated by any other condition. If one is in doubt resort may be had to exercise or to the increase in rate produced by amyl nitrite or atropine such procedures usually abolish the arrhythmia of sinoatrial or premature beat origin and increase that of atrial fibrillation. Besides differing from atrial flutter and paroxysmal tachycardia in rhythm atrial fibrillation differs from these disorders further in that it is more often a permanent and less often a paroxysmal state and in that it more often occurs with definite indications of organic heart disease also and more readily responds to quinidine and digitalis therapy.

### ATRIAL FLUTTER

Atrial flutter due to a disorder of atrial mechanism closely related to that of fibrillation but usually with regular rapid ventricular action is uncommon. It was named by Jolly and Ritchie in 1911.

**Incidence** Atrial flutter is probably not so rare as statistics indicate since shorter paroxysms may easily be missed or considered to be paroxysmal tachycardia in the absence of graphic records. When it is recognizable without

graphic records atrial flutter is found only about twice to every fifty cases of atrial fibrillation. When electrocardiograms are routinely taken atrial flutter is found about once for every 14 cases of atrial fibrillation. Thus we found 104 cases of atrial flutter and 1 422 cases of atrial fibrillation among 10 000 patients electrocardiographed at the Massachusetts General Hospital from 1914 to 1931 (White and Sprague 1931).

**Mechanism (abnormal physiology)** Atrial flutter is characterized by regular but abnormal atrial contractions at a very rapid rate and usually by regular ventricular contractions at one half the atrial rate. The atrial rate ranges from 200 or slightly less to 400 or slightly more with an average of 300 per minute. The ventricular rate is often exactly one half the atrial rate because of 2 to 1 atrioventricular block; sometimes it is slower than that or irregular due to greater or varying grades of block and rarely it is the same as the atrial rate due to the absence of block, this last mentioned state often being called 1 to 1 rhythm. Generally conduction within the ventricles themselves is normal but with very rapid rates functional intraventricular (bundle branch) block may occur, disappearing later when the rate falls or the atrial flutter stops. Very rarely complete heart block may be associated with atrial flutter.

The mechanism of atrial flutter is not yet perfectly clear. Like atrial fibrillation flutter has been for many years ascribed to a circus movement (Lewis et al 1920) but recently doubt has been cast on this mechanism as noted earlier in this chapter (Scherf et al 1948 Prinzmetal et al 1949) (see page 896) and an alternative proposed of rapid excitation from an irritable focus in the atria as in paroxysmal tachycardia. If the path is shortened or its speed increased the atrial rate per minute increases and if this exceeds 400 per minute it becomes irregular. When the excitatory process becomes very rapid and irregular it is no longer called atrial flutter but atrial fibrillation; there is a wide boundary between the two clear cut conditions which may be termed flutter fibrillation. Although atrial flutter and atrial fibrillation are closely allied in mechanism their separation is useful and important from the clinical standpoint.

Atrial flutter has sometimes been regarded clinically as midway between atrial paroxysmal tachycardia and atrial fibrillation but it is much more closely related to the latter as evidenced for example by the electrocardiogram which in the case of atrial flutter shows constant movement of the baseline due to atrial activity (Figure 159) while in atrial paroxysmal tachycardia there are short atrial waves sharply differentiated and separated from each other (Figure 156 page 879).

Atrial flutter like fibrillation may be paroxysmal or permanent. It is much more likely to be paroxysmal, the paroxysms lasting usually for hours to days occasionally for weeks and rarely for months or years. Paroxysmal atrial flutter occurs in three or four times as many cases as does permanent atrial flutter.

**Etiology Cause** The precise way in which atrial flutter is started is not clear but predisposing conditions are for the most part known. Like atrial

fibrillation atrial flutter is more commonly found in the presence of heart disease than in its absence. It is especially likely to occur in mitral stenosis, hypertension, thyrotoxicosis, and coronary heart disease, but it exists sometimes alone with no evidence of heart disease or any other pathologic condition. An otherwise perfectly healthy strong person may have atrial flutter. Whether it is the only abnormality or one associated with serious disease, it is commonly precipitated by sudden effort, nervous excitement, trauma, or surgical operation, particularly involving the thorax; rarely it begins without apparent provocation.

Lead

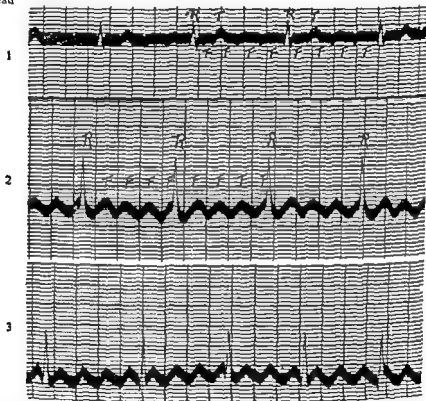


FIG. 159. Electrocardiogram showing atrial flutter. Three leads. Four to one and three to one atrioventricular block.

In a series of 52 cases of atrial flutter observed by Parkinson and Bedford (1927) between the years 1913 and 1926 there were the following etiologic findings: chronic rheumatic heart disease in 14 cases (27 per cent), acute rheumatic infection in 2 cases, other acute febrile illnesses in 3, thyrotoxicosis in 2, hypertension in 6, myocardial infarction in 3, a positive Wassermann reaction in 3, cardiac enlargement other than rheumatic, hypertensive or syphilitic in 13, congenital heart disease in 1, and no evidence of heart disease in 5. Of the 14 cases of chronic rheumatic heart disease, 7 showed mitral

stenosis alone 4 mitral stenosis and aortic regurgitation 2 mitral disease without clinical evidence of stenosis and 1 aortic regurgitation alone

**Sex** The sexes are represented unequally in statistics so far available the male sex preponderating in about the ratio of 3 to 1 The cause for this difference is not clear except that the male sex is generally under greater strain than the female sex

**Age** The incidence of atrial flutter is much greater in later decades of life than in youth three fourths of the cases occurring after the age of forty years However it is encountered in children and even in infants

**Pathology** There are no known structural changes in the myocardium characteristic of atrial flutter There may be extensive heart disease or there may be none the abnormal finding more often noted than any other in a heart with atrial flutter is mitral stenosis

**Symptoms** The typical symptom of atrial flutter is rapid regular forceful palpitation sometimes described by the patient himself as heart flutter but not distinguishable in sensation from paroxysmal tachycardia There may or may not be symptoms of congestive failure coincident with or in some cases induced by the atrial flutter congestive failure is likely to occur if the atrial flutter is of long duration in persons with damaged hearts Pain is rare precordial aching may occur The alarm occasioned by the atrial flutter may be so great that much nervous excitement and even a state of nervous prostration may exist If the ventricular rate is very rapid as sometimes happens when there is no block (1:1 rhythm) and the heart rate approaches 300 per minute weakness dizziness faintness or even actual syncope may occur associated with cerebral anemia and other effects of the very small output of blood and much reduced blood flow

**Signs** The characteristic sign of atrial flutter is the regular rapid heart rate which is maintained often with variations of but a few beats from minute to minute for days weeks or months at a time in spite of exercise rest and sometimes even drug therapy The apex rate and usually also the radial pulse rate average about 150 per minute while electrocardiograms show double this rate for the atrial action (about 300 per minute) in approximately half of the cases of atrial flutter when first seen Sometimes the heart rate is found to be irregular even before treatment due to varying grades of block usually 1:1 2:1 3:1 or 4:1 coming in regular or quite irregular sequences so that the arrhythmia may be an orderly one or a very disorderly one Sometimes the heart rate is regular and very fast (with 1:1 rhythm) or regular and slow (with 3:1 4:1 6:1 or even 8:1 block regularly maintained) These variations of block thus account for that half of the cases of atrial flutter without a constant 2 to 1 block Although great and irregular variation of grades of atrio-ventricular block may produce a heart action that seems on cardiac auscultation or on palpation of the pulse to be absolutely irregular careful study and especially measurement of the arteriogram will show the existence of a dominant rhythm whereby for example four pulse intervals of 2 to 1 block will equal in duration two pulse intervals of 4 to 1 block this finding of a definite

dominant rhythm rules out atrial fibrillation even without an electrocardiogram but the measurements are sometimes difficult and obscure. Some cases that happen to have atrial flutter with an atrial rate of about 300 and 4 to 1 heart block which occurs either spontaneously or after treatment are almost sure to escape notice clinically because of their regular slow heart action and pulse rate of about 75 unless phlebograms or electrocardiograms are taken. This infrequent but important happening is a further illustration of the value of graphic records (see Figure 159, page 914).

Related to the natural tendency for atrial flutter to show a  $v$  block is a clinical test for this disorder of rhythm. It is the rule for firm pressure by the fingers over the carotid sinus on either side of the neck to increase the grade of block and so to slow the heart rate to one half or even less during the application of the pressure, the fast and regular rate quickly returning on release of the pressure to its original high level. Thus a ventricular rate of 150 with 2 to 1 block in atrial flutter can drop to 75 with the change to 4 to 1 block. Such a change does not occur in sinus tachycardia while if a sharp drop of heart rate occurs in the case of atrial paroxysmal tachycardia when pressure is applied to the carotid sinus it means that the paroxysm has been abolished and so the rate does not go up again directly the carotid sinus pressure is released.

In doubtful cases when atrial flutter is possible or suspected electrocardiograms should be obtained; they are far superior to clinical signs or tests and to phlebograms because they not only reveal the atrial action more clearly but they distinguish at once between atrial flutter and atrial paroxysmal tachycardia and moreover they afford other information about the cardiac mechanism. The flutter waves produced in the electrocardiogram by the atrial action are best shown by a special lead with exploring electrode over the third intercostal space just to the right of the sternum; they are almost always well seen in Leads 2 and 3 but are often so poorly marked in Lead 1 and in the routine precordial leads over the right and left ventricles ( $V_1$  to  $V_6$  inclusive) that the interpretation from these leads may remain in doubt.

Roentgen ray study in atrial flutter is of relatively little value although in some cases the abnormal mechanism may be observed fluoroscopically.

With atrial flutter there may or may not be signs of cardiac enlargement, valvular disease, pericarditis, aortic disease, hypertension or congestive failure; in half the cases or more there are such signs.

Special tests may show a decreased blood flow when the heart rate is very rapid but this will return to normal when the ventricular rate falls if there is no heart failure. With very fast heart rates the systolic blood pressure also tends to be low (100 mm or less) and the pulse pressure small (20 to 30 mm).

**Course and prognosis.** Clinically atrial flutter falls midway between atrial paroxysmal tachycardia and atrial fibrillation as regards significance and duration. It is more important than paroxysmal tachycardia because it is found more often with heart disease and lasts longer but it is somewhat easier to

control. It is somewhat less important than atrial fibrillation because it is less often permanent and is less likely to be associated with serious heart disease. The heart rate is however harder to control. Generally atrial flutter lasts for hours, days or weeks, rarely for minutes, months or years. We have observed an instance of atrial flutter lasting five years with ventricular rate for most of the time at 130 per minute (2 to 1 atrioventricular block) or 260 (1:1 rhythm) not responding to treatment but stopping spontaneously and leaving no trace of heart disease (Sprague and White, 1928). Lewis has known atrial flutter to last uninterruptedly for twenty-four years, the ventricles beating without cessation at 140 per minute (Lewis, 1937) and Kossman and Berger (1941) have reported an instance of eleven years' duration. We have had another case under our own observation for twenty-six years who is still in good health with no other evidence of heart trouble than the persistent atrial flutter.

The condition starts abruptly and usually either stops abruptly or changes suddenly or slowly to atrial fibrillation. The ventricular rate usually falls through increase of the grade of heart block under digitalis therapy. It often is a disagreeable and more or less crippling condition, but it is rarely dangerous. In a few cases, generally with serious heart disease, atrial flutter of long duration and not yielding to treatment leads to heart failure and may even cause death.

**Complications.** Congestive heart failure, atrial thrombosis and embolism may occur as complications of atrial flutter, but they are less common than in the case of atrial fibrillation.

**Treatment.** Atrial flutter is more amenable to digitalis therapy than to quinine therapy, and it is wiser to use digitalis than any other drug in the treatment of established flutter. If there is but a brief paroxysm lasting a few minutes or at most a few hours, no treatment at all may be necessary other than rest and reassurance.

When atrial flutter has lasted for more than a few hours, digitalis therapy should be started, preferably 0.2 gm (3 gr) of the standardized powdered leaf or digitoxin 0.2 to 0.3 mg by mouth, three times a day for two or three days as needed. In emergencies when the tachycardia associated with the flutter causes great distress or myocardial failure, the digitalis can, of course, be given intravenously as described for atrial fibrillation earlier in this chapter (see page 905). If the atrial flutter persists after three days but the ventricular rate has been reduced to normal figures by increase in the grade of block (4 to 1 or more), the digitalis leaf may be reduced to a daily ration of 0.06 or 0.1 gm (1 or 1½ gr) or the digitoxin to 0.1 to 0.2, perhaps best 0.15 mg, to maintain the full drug effect so long as is necessary. If atrial fibrillation has been induced, the digitalis may be continued to maintain a slow ventricular rate or it may be dropped to see whether or not normal rhythm will soon follow as it sometimes does. This latter was once thought to be the usual (classical) course. When normal rhythm does return, the continuance of

treatment is not necessary except for the avoidance of factors which may induce a return of the atrial flutter and a prophylactic dose of quinidine sulfate 0.2 gm (3 gr) four times a day for a few days may be used.

Quinidine sulfate may be administered in the way described for atrial fibrillation earlier in this chapter to cases not responding to digitalis or to cases believed amenable to quinidine for the purpose of restoring normal rhythm at the outset or after the atrial fibrillation into which it is converted has become fixed whether or not there is a slowing of the heart rate by digitalis.

In about half the cases of atrial flutter digitalis therapy is successful in another few cases quinidine is successful when digitalis fails in others digitalis is partly successful in that a satisfactorily slow heart rate is produced although atrial flutter or fibrillation continues and in rare cases neither digitalis nor quinidine controls either the atrial mechanism or the ventricular rate the attack of flutter stopping spontaneously perhaps after months or even years. The best course generally to pursue is first to digitalize the patient with atrial flutter and then if normal rhythm is not restored to try a course of quinidine sulfate.

Complications of atrial flutter like congestive failure demand treatment as much as does the disturbance of heart rhythm digitalis is especially valuable in this respect for it is the best therapy for both the atrial flutter and the congestive failure. If the situation is urgent the drug may be given intravenously as stated above.

Finally to prevent paroxysms of atrial flutter or a recurrence of permanent flutter care should be taken to avoid exciting factors—fatigue physical or mental sudden exertion overeating excessive use of tobacco alcohol tea or coffee infections focal or general unnecessary surgical operations and congestive heart failure. Rations of quinidine sulfate 0.2 gm (3 gr) three or four times a day or of digitalis 0.06 or 0.1 gm (1 or 1½ gr) daily after digitalization are also sometimes effective just as they are in reducing the number and duration of paroxysms of tachycardia or of atrial fibrillation such drugs should be used as needed but not necessarily as a routine in every case.

**Differential diagnosis** Atrial flutter is to be differentiated from sinoatrial tachycardia paroxysmal tachycardia and atrial fibrillation. Its long duration with rapid steady heart rate under various circumstances the absence of fever thyrotoxicosis and excitement which might be responsible for sinoatrial tachycardia and the frequent presence of heart disease help to distinguish atrial flutter from rapid normal rhythm. The long duration of the paroxysms of atrial flutter the more common association with heart disease and the tendency of carotid sinus pressure to slow the heart rate temporarily by increasing the grade of block but not to abolish the abnormal rhythm distinguish flutter clinically from paroxysmal tachycardia. The regularity of rhythm is the essential characteristic which ordinarily differentiates flutter from fibrillation. It is often necessary however and always wise to obtain an electrocardiogram to be sure of the diagnosis of atrial flutter.

## VENTRICULAR FIBRILLATION AND FLUTTER

*Ventricular fibrillation* consists of an apparently incoordinated ventricular action with cessation of regular contraction resulting in death if effective ventricular action is not speedily resumed. It was first noted in 1850 by Hoffa and Ludwig in the laboratory. As a temporary or terminal condition it is frequently seen in experimental animals as in the dog and cat and it has occasionally been encountered in human electrocardiograms in dying patients. It probably is commonly a terminal condition in man but an actual cause of death only under certain circumstances as in fatalities resulting from the blocking of the coronary circulation and in death during chloroform anesthesia from acute benzol poisoning and from electrocution which procedures have been shown to cause ventricular fibrillation in experimental animals and in rare instances in man. The smaller the heart in experimental animals the greater the chance for restoration of normal rhythm the human heart may be too large to permit frequent recovery even if ventricular fibrillation were of frequent occurrence.

A number of human electrocardiograms showing ventricular fibrillation have been published but the separation electrocardiographically between ventricular fibrillation and ventricular paroxysmal tachycardia and flutter is not a sharp one and the interpretation is sometimes in doubt. A clear-cut instance is shown in Figure 160.

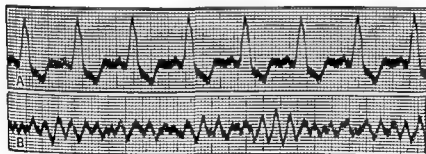


FIG 160 Electrocardiograms of a case with bundle branch block (A) who died in an attack of ventricular fibrillation (B) (Graybiel and White *Electrocardiography in Practice* 1941 Kindness of W B Saunders Company Philadelphia)

The mechanism of ventricular fibrillation is obscure it may be similar for the ventricles to that of atrial fibrillation for the atria it may consist of an irregular circus movement or there may be multiple spread or foci of ventricular activity.

The relationship of the mechanisms of ventricular paroxysmal tachycardia and ventricular fibrillation seems close the former tending to evolve into the latter via an intermediate mechanism *ventricular flutter* which has been discussed recently by Fastier and Smirk (1948) and which is very rapid but



regular One of the most authoritative opinions concerning the pathologic physiology or mechanism of ventricular fibrillation is that presented by Wiggers in 1940 After stating that the process is an evolution of changes from the moment of its inception until it ceases completely in the course of 30 to 45 minutes Wiggers writes that the available evidence favors the conclusion that after a single premature systole the phenomenon is caused by re-entry of circulating wave fronts which involve smaller and smaller blocks of myocardium each of which develops an independent excitation As a result of the anoxia which develops progressively after the cessation of coronary flow conduction is slowed and the vigor of fractionate contractions decreased The resultant of these changes causes in succession the undulatory convulsive tremulous and atonic stages of its evolution Wiggers has been able to carry out defibrillation experimentally in dogs by passing strong alternating currents for brief intervals of 0.1 to 5 seconds through the ventricles provided such countershock is applied within approximately two minutes Application of comparable electric shock by chest electrodes to man would Wiggers states be dangerous to both operator and patient Massage of the heart in the case of dogs with more prolonged asystole has aided in the recovery of the heart by the countershocks

Clinically ventricular fibrillation and flutter are conditions of uncertain importance in the present state of our knowledge They have been encountered after massive doses of digitalis and after epinephrine (adrenaline) as an end stage of ventricular paroxysmal tachycardia and in a few patients dying with other conditions They are probably commonly a terminal event after coronary thrombosis and during chloroform anesthesia and electrocution They are also a hazard in cyclopropane anesthesia They have been noted in rare cases dying of angina pectoris while being electrocardiographed and have been found in individuals dying of some infectious diseases However they are not the only mechanism of heart death depression of the pacemakers and of atrio-ventricular conduction being found more often Syncope transient or leading to death and simulating the Adams Stokes syndrome has been reported in several cases of prolonged ventricular fibrillation it is always very ominous Recovery has been rare

It is probable that quinidine sulfate does help to prevent fibrillation of the ventricles if given in moderate dosage to individuals threatened with this usually fatal arrhythmia especially in cases of recent myocardial infarction or those subject to paroxysms of ventricular tachycardia but as yet we have no certainty of this Borg (1939) suggested its use in all cases of coronary insufficiency and believes that he reduced the mortality in coronary heart disease thereby My own experience makes me think that he is right but adequate statistical proof is still lacking Acetylcholin (acetyl B methylcholin chloride) and papaverine have been shown in experimental animals to act prophylactically (Nahum and Hoff 1934 and Lindner and Katz 1941 respectively)

In the last edition of this book it was stated that there was no specific

therapy once ventricular fibrillation has begun. However Beck et al (1941 and 1947) have demonstrated that if the heart is exposed an electric shock of 110 volts and 1.15 amperes can restore the normal heartbeat. They have reported success in one case of ventricular fibrillation of long duration.

## BIBLIOGRAPHY

ATRIAL FIBRILLATION AND FLUTTER, VENTRICULAR FIBRILLATION  
AND FLUTTER QUINIDINE THERAPY

Atrial Fibrillation (See also General References following Chapter 2 and references under Atrial Flutter below)

- Barber E W and Middleton R P "Auricular Fibrillation in Childhood: Report of Cases" *Am J Dis Child* 1928 XXXV 40
- Blumgart H "The Reaction to Exercise of the Heart Affected by Auricular Fibrillation" *Heart* 1924 XI 49
- Brill I C "Auricular Fibrillation with Congestive Failure and No Other Evidence of Organic Heart Disease" *Am Heart J* 1937 XIII 175
- Burch G E "Auricular Fibrillation of 22 Months Duration with Return to Normal Sinus Mechanism without the Aid of Quinidine" *Am Heart J* 1939 XVIII 102
- Comeau W J "A Mechanism for Syncopal Attacks Associated with Paroxysmal Auricular Fibrillation" *New England J Med* 1942 CCXXVII 134
- Cushny A R and Edmunds C W "Paroxysmal Irregularity of the Heart and Auricular Fibrillation" *Studies in Pathology* (edited by Bulloch) Aberdeen 1906 XXI 95 and *Am J M Sc* 1907 CXXXIII 66
- Fogel M "Auricular Fibrillation of Long Standing with Spontaneous Return to Normal Sinus Rhythm" *Am Heart J* 1943 XXV 700
- Fowler W M and Baldrige C W "Auricular Fibrillation as the Only Manifestation of Heart Disease" *Am Heart J* 1930 VI 183
- Fox, G H "The Clinical Significance of Transitory Delirium Cordis" *Am J M Sc* 1910 CXL 815
- Friedlander R D and Levine S A "Auricular Fibrillation and Flutter Without Evidence of Organic Heart Disease" *New England J Med* 1934 CCXI 64
- Frothingham C "The Auricles in Cases of Auricular Fibrillation" *Arch Int Med* 1925 XXXVI 437
- Garrey W E "The Suppression of Cardiac Fibrillation by Section" *Interstate M J* Chicago 1912 XIX 1081
- "The Nature of Fibrillary Contraction of the Heart—Its Relation to Tissue Mass and Form" *Am J Physiol* 1914 XXXIII 397
- "Auricular Fibrillation" *Physiol Rev* 1924 IV 215
- Hay J and Jones H W "Trauma as Cause of Auricular Fibrillation: Its Medico Legal Significance" *Brit M J* 1927 I 559
- Heitz J "Un cas d'arythmie complète permanente évoluant depuis trente-deux ans" *Arch d mal d cœur* 1914 VII 116
- Hering H E "Analyse des Pulsus irregularis perpetuus" *Prager med Wchnschr* 1903 XXVIII 377
- "Ueber den Pulsus irregularis perpetuus" *Deutsch Arch f klin Med* 1908 XCIV 185
- Lewis T "Auricular Fibrillation: A Common Clinical Condition" *Brit M J* 1909 II 1578
- Lewis T, Drury A N and Ilescu C C "A Demonstration of Circus Movement in Clinical Fibrillation of the Auricles" *Heart* 1921 VIII 361
- Leyes D G and Russell H B "A Case of Persistent Auricular Fibrillation in a Child of Six" *Lancet* 1927 II 702
- McEachern D and Baker H M Jr "Auricular Fibrillation: Its Etiology, Age Incidence and Production of Digitalis Therapy" *Am J M Sc* 193 CLXXXIII 35

- Mackenzie J "The Interpretation of the Pulsations in the Jugular Veins" *Am J M Sc* 1907 CXXXIV 12
- Mayer A G Rhythmic Pulsation in Scyphomedusae *Papers from the Dept of Marine Biology of the Carnegie Institute of Washington* 1908 p 115
- Mines G R On Circulating Excitations in Heart Muscle and Their Possible Relation to Tachycardia and Fibrillation *Tr Roy Soc Canada* 1914 Series 3 VIII 43
- Orgain E S Wolff L and White P D Uncomplicated Auricular Fibrillation and Auricular Flutter Frequent Occurrence and Good Prognosis in Patients without Other Evidence of Cardiac Disease *Arch Int Med* 1936 LVII 493
- Parkinson J and Campbell M Paroxysmal Auricular Fibrillation A Record of Two Hundred Patients *Quart J Med* 1930 XXIV 67
- Phillips E and Levine S A Auricular Fibrillation without Other Evidence of Heart Disease A Cause of Reversible Heart Failure *Am J Med* 1949 VII 478
- Pinchenon B *La Derivation Auriculaire SS et la Trémulation Auriculaire* J B Baillière et Fils Paris 1937
- Robinson G C Transient Auricular Fibrillation in a Healthy Man Following Hydrogen Sulphide Poisoning *JAMA* 1916 LXVI 1611
- Rotherberger C J and Winterberg H Vorhoffimmern und Ahythmia perpetua *Wien klin Wchnschr* 1909 XXII 839
- White P D and Jones T D Heart Disease and Disorders in New England *Am Heart J* 1928 III 302
- Wolff L Familial Auricular Fibrillation *New England J Med* 1943 CCXXIX 396

#### Recent References (1944-1950)

- Hanson H H and Rutledge D I Auricular Fibrillation in Normal Hearts *New England J Med* 1949 CCXL 947
- Hanssen P "The Incidence of Auricular Flutter and Auricular Fibrillation Associated with Complete Auriculo-ventricular Dissociation" *Acta med Scandinav* 1949 CXXXVI 112
- Knox J A C The Heart Rate with Exercise in Patients with Auricular Fibrillation *Brit Heart J* 1949 XI 119
- Lian C and Gerbaux A La fibrillation auriculaire par électrocution *Arch des mal du coeur* 1948 XLI 423
- Wright I S et al Ball Thrombus in the Right Auricle of the Heart with a Description of the Symptoms Produced *Am Heart J* 1944 XXVII 858

#### Atrial Flutter

- Jolly W A and Ritchie W T Auricular Flutter and Fibrillation *Heart* 1911 II 177 (Introduction of the expression auricular flutter)
- Kossman C E and Berger A R Auricular Flutter of Eleven Years Duration with Observations on Esophageal Electrocardiograms *Ann Int Med* 1941 XV 178
- Lewis T Observations Upon a Curious and Not Uncommon Form of Extreme Acceleration of the Auricle Auricular Flutter *Heart* 1912-13 IV 171
- Auricular Flutter Continuing for Twenty Four Years *Brit M J* 1937 I 1748
- Lewis T Feil H S and Stroud W D Observations upon Flutter and Fibrillation Part II The Nature of Auricular Flutter *Heart* 1920 VII 191
- Parkinson J and Bedford D E The Course and Treatment of Auricular Flutter *Quart J Med* 1927 XXI 21
- Ritchie W T *Auricular Flutter* W Green & Son Ltd Edinburgh and London 1914
- Sprague H B and White P D Auricular Flutter Report of a Case of Five Years Duration with Spontaneous Restoration of Normal Rhythm *JAMA* 1928 XC 1772
- White P D and Sprague H B Electrocardiography of 10 000 Patients at the Massachusetts General Hospital from 1914 to 1931 *Kasan Med Jour USSR* 1931 XXVII 381

#### Recent References (1944-1950)

- Fenichel N M Chronic Auricular Flutter *Ann Int Med* 1948 XXIX 144
- Hejtmancik M R Herrmann G R and Bradfield J Y "Atrial Flutter I Clinical Aspects" *Am Heart J* 1950 XL 884

- Herrmann G R and Heytmancik M H "Atrial Flutter II Methods of Treatment" *Am Heart J* 1951 XLI 182
- Lenegre J and Mathivat A "Le flutter auriculaire (à propos de 50 observations personnelles)" *La Semaine des H p de Paris* 1947 XXIII 2225
- Prinzmetal M Brill I C Corday E Sellers A L Fleg W A and Kruger H E "The Nature of Auricular Flutter" *J Clin Investigation* 1949 XXVIII 804
- Scherf D Romano F J and Terranova R "Experimental Studies on Auricular Flutter and Auricular Fibrillation" *Am Heart J* 1948 XXXVI 241

### Ventricular Fibrillation and Flutter

- Beck C S "Resuscitation from Cardiac Standstill and Ventricular Fibrillation Occurring During Operation" *Am J Surg* 1941 LIII 73
- Borg J "Observations on the Occurrence and Prevention of Sudden Death" *Tr Am Therap Soc* 1939 XXXIX 115
- Hamilton R L and Robertson H "Electrocardiographic Studies of the Dying Heart in Angina Pectoris" *Canad M J* 1933 XXIX 122
- Hering H E "Der Sekundenherz tod mit besonderer Berücksichtigung des Her kammer flimmerns" Julius Springer Berlin 1917
- Hoffa M and Ludwig C "Einige neue Versuche über Herzbewegung" *Ztschr f rat Med* Heidelberg 1850 IX 107
- Lindner E and Katz, L N "Papaverine Hydrochloride and Ventricular Fibrillation" *Am J Path* 1941 CXXXIII 155
- MacWilliam J A "Fibrillar Contraction of the Heart" *J Physiol* 1887 VIII 296
- Some Applications of Physiology to Medicine II: Ventricular Fibrillation and Sudden Death" *Brit M J* 1923 II 215
- N hum L H and Hoff H F "The Mechanism of Sudden Death in Experimental Acute Benzol Poisoning" *J Pharmacol & Exper Therap* 1934 L 336
- Observations on Potassium Fibrillation" *Ibid* 1939 LXV 322
- Wiggers C J "The Mechanism and Nature of Ventricular Fibrillation" *Am Heart J* 1940 XX 399
- "The Physiologic Basis for Cardiac Resuscitation from Ventricular Fibrillation—Method for Serial Defibrillation" *Am Heart J* 1940 XX 413

### Recent References (1944-1950)

- Beck C S Pritchard W H and Feil H S "Ventricular Fibrillation of Long Duration Abolished by Electric Shock" *JAMA* 1947 CXXXV 985
- Bechgaard P "Paroxysmal Ventricular Fibrillation with Recovery" *Acta med scand* 1948 CXXXII 9
- Daniel F D and Magruder R G "Report of a Case of Ventricular Fibrillation with Recovery Following Acute Coronary Occlusion" *Am Heart J* 1950 XXXIX 451
- Faster F N and Smirk F H "Some Properties of Amaryn with Special Reference to Its Use in Conjunction with Adrenaline for the Production of Idio Ventricular Rhythms" *J Physiol* 1948 CVII 318
- Fauteux M "Preventive Treatment of Ventricular Fibrillation in Course of Coronary Disease Experimental Study" *Union Med du Canada* 1946 LXXV 368
- Horowitz W and Burstein J "Ventricular Fibrillation Persisting Thirty Minutes After Clinical Death" *New York State J Med* 1946 XLVI 914
- Kunkel A M Oikemus A H and McNamara H P "Acetylcholine induced Ventricular Fibrillation" *J Pharmacol & Exper Therap* 1951 CI 22
- Lampson R S Schaeffer W C and Lincoln J R "Acute Circulatory Arrest from Ventricular Fibrillation for Twenty Seven Minutes with Complete Recovery" *JAMA* 1948 CXXXVII 1575
- Priest W M "Ventricular Fibrillation Recorded Ten Hours Before Death from Myocardial Infarction" *Lancet* 1949 II 699
- Storstein O "Stokes Adams Attacks Caused by Ventricular Fibrillation in a Man with Otherwise Normal Heart" *Acta med Scandinav* 1949 CXXXIII 437
- Quinidine and Substitutes
- Frey W "Ueber Vorhofflimmern beim Menschen und seine Beseitigung durch Chinidin" *Berlin klin Wchnschr* 1918 LV 417 and 450

- Lewis T Drury A N Iliescu C C and Wedd A M "The Manner in Which Quinidine Sulphate Acts in Auricular Fibrillation" *Brit M J* 1921 II 514
- Senac J B *Traité de la Structure du Cœur de son Action et de ses Maladies* J Vincent Paris 1749 Vol 2 p 526
- Sturnick M I "An Unusual Toxic Manifestation of the Oral Use of Quinidine Sulfate" *Am Heart J* 1942 XXIV 559
- Trousseau V "Remarques sur une formule de sirop de quinquina rouge ferrugineux" *Bull gén de thérap Paris* 1863 I XV 454
- Weisman S A "Quinidine Pure Quinidine and Hydroquinidine I Toxicity" *Am Heart J* 1942 XXIV 545
- Wenckebach K F "Die Therapie des Vorhofflummerns" Page 125 of *Die unregelmässige Hertätigkeit und ihre klinische Bedeutung* W Engelmann Leipzig and Berlin 1914
- White P D and Blumgart H "Cessation of Repeated Pulmonary Infarction and of Congestive Failure after Termination of Auricular Fibrillation by Quinidine Therapy" *J Mt Sinai Hosp* 1942 VIII 1095
- Wolff L and White P D "Auricular Fibrillation Results of Seven Years Experience with Quinidine Sulphate Therapy (1921 to 1928)" *Arch Int Med* 1929 XLIII 65
- "Auricular Standstill During Quinidine Therapy" *Heart* 1929 XIV 295

#### Recent References (1944-1950)

- Alexander F Gold H Katz L N and others "Relative Value of Synthetic Quinidine Dihydroquinidine Commercial Quinidine and Quinine in the Control of Cardiac Arrhythmias" *J Pharmacol and Exper Therap* 1947 XC 191
- Carlotti J and White P D "Surveillance durant une période d'un an de l'usage de la quinidine au Massachusetts General Hospital (Boston) Discussion des indications et des résultats" *Arch des mal du cœur* 1948 XLI 225
- Deulofeu V Labriola Orias O Moisset de Espanes E and Taquini A "Fagarine A Possible Substitute for Quinidine" *Science* 1945 CII 69
- DiPalma J R and Schultz J F "Antifibrillatory Drugs" *Medicine* 1950 XXIX 123
- Feibush J S and Greenberg D "Electrocardiographic Study of Intramuscular Quinidine Lactate" *Am Heart J* 1950 XL 585
- Ferrer M I Harvey R M Werko L Dresdale D T Courmand A and Richards D W Jr "Some Effects of Quinidine Sulfate on the Heart and Circulation in Man" *Am Heart J* 1948 XXXVI 816
- Gertler M M and Yohalem S B "The Effect of Atabrine (Quinacrine Hydrochloride) on Cardiac Arrhythmias" *Am Heart J* 1949 XXXVII 79
- Kalfmansohn R W and Sampson J I "Studies of Plasma Quinidine Content I Relation to Single Dose Administration by Three Routes" *Circulation* 1950 I 564
- II "Relation to Toxic Manifestations and Therapeutic Effect" *Ibid* 569
- Laake H "Experiences with Quinidine Treatment of Auricular Block" *Nord med* 1945 XXVI 820
- McMillan R L and Welfare C R "Chronic Auricular Fibrillation Its Treatment with Quinidine Sulfate" *JAMA* 1947 CXXXV 1132
- Scherf D Silver A M and Weinberg L D "Clinical Observations with Fagarine" *Ann Int Med* 1949 XXX 100
- Siegal S and Horn H "Quinidine Allergy" *Am Heart J* 1950 XXXIX 302
- Sokolow M and Edgar A L "Blood Quinidine Concentrations as a Guide in the Treatment of Cardiac Arrhythmias" *Circulation* 1950 I 576
- Taquini A C "Fagarine—A New Drug for the Treatment of Auricular Fibrillation and Flutter" *Am Heart J* 1947 XXXIII 719
- Wegria R "Intensity and Duration of Action of Quinidine Sulfate in Auricular Fibrillation and Flutter" *Am Heart J* 1948 XXXV 787

---

## CHAPTER 34

---

# BRADYCARDIA AND HEART BLOCK (SINOATRIAL, ATRIOVENTRICULAR, AND INTRAVENTRICULAR) VENTRICULAR ESCAPE ATRIOVENTRICULAR NODAL RHYTHM SUDDEN DEATH

---

Heart block in its various manifestations the subject of the present chapter is primarily the result of depression of the specialized tissues that normally initiate the heartbeat (sinoatrial and atrioventricular nodes) and conduct it to the muscle of both ventricles (atrioventricular bundle and its branches) in contrast to the abnormal cardiac rhythms due to unusual excitability and stimulation that have been considered in the last two chapters. When the sinoatrial node is much depressed we have *sinoatrial block* often with control of the heartbeat by the atrioventricular node; if this lower nodal pacemaker initiates occasional beats we speak of *ventricular escape*; if it controls the ventricular rhythm entirely we speak of an *idioventricular rhythm*; and when it controls atrial as well as ventricular action with sinoatrial node wholly silent we speak of *atrioventricular nodal rhythm*. Delay or more or less complete blocking of the impulse (initiated by the sinoatrial node) in the atrioventricular node and bundle gives rise to *atrioventricular block* while delay or blocking of the impulse in the bundle branches causes *intra-ventricular block* or *bundle branch block*. The immediate causes (mechanisms) of sudden death are (1) complete depression of both nodes, (2) a complete blocking of the atrial impulse above the ventricular muscle with paralysis of the lower nodal and bundle pacemaker and (3) ventricular fibrillation (see Chapter 33 for this last named disorder).

### SINOATRIAL BRADYCARDIA SINUS ARRHYTHMIA AND BLOCK. ATRIAL STANDSTILL VENTRICULAR ESCAPE

**Mechanism** If the normal pacemaker the sinoatrial node is depressed the heart rate slows. *sinoatrial bradycardia* is the term applied to this slowing of

the whole heart. Often associated with the bradycardia is *sinus arrhythmia* (Figure 161A). If it happens that occasionally or frequently there appears between atrial beats an interval which is equal or almost equal to two usual cycles the condition is called *partial sinoatrial block* if the atrial rate becomes very slow (35 or less per minute) whether regular (as it usually is) or irregular the condition is sometimes termed *high grade sinoatrial block* and if the atrial contractions drop out altogether the ventricles continuing to beat as the result of independent stimulation from the atrioventricular node a condition results which has been called *complete sinoatrial block*, *atrial stand still* or *atrial paralysis*.

**Incidence.** *Sinoatrial bradycardia* is normal and unimportant except when of extreme degree that is when the whole heart rate sinks below 35 or less per minute. A sinoatrial rate of 50 or 60 is common in many normal individuals at rest sometimes during sleep or on first waking in the morning the heart rate may be as slow as 45. Sinoatrial bradycardia can frequently be produced by *vagal stimulation* most readily by pressure over the right *carotid sinus* in normal persons or in patients whose heart rate is already rather slow and especially if digitalis has been previously given in moderate or large dosage. Occasionally in a normal person carotid sinus pressure may slow the heart excessively and faintness and even syncope have been caused by such tests especially if the carotid sinus is sensitive. If the pulse is fast usually because of sympathetic nerve stimulation carotid sinus pressure is much less effective except in a few cases when it may abolish paroxysmal tachycardia or increase the grade of heart block already present in atrial flutter. Pressure on the left side of the neck and on the eyeballs (oculocardiac reflex) may also slow the heart by causing depression of the sinoatrial pacemaker through vagal stimulation but pressure in such places is usually less effective than right carotid sinus pressure. Voluntary slowing unlike voluntary acceleration of the heart rate is not directly possible, the individuals who have been reported to have slowed their pulse voluntarily have apparently caused bradycardia reflexly by respiratory effort or have obliterated their radial pulse by muscular movements of the thorax mainly by an upward and backward shrugging of the shoulders thereby compressing the subclavian arteries. Athletes sometimes show an abrupt fall in heart rate even a halving shortly after the completion of some special effort this apparently is a normal vagal reaction which tends to be much accentuated by training.

It is very important to remember that a heart rate in the forties or even in the thirties per minute at rest can be a perfectly normal occurrence especially in athletes in training and particularly in distance runners (White 1942).

**Etiology Cause.** Pathologic degrees of sinoatrial bradycardia block and arrhythmia are seen rarely. They are most commonly produced by digitalis in excessive dosage and in individuals whose tolerance for the drug is low. Other drugs of the digitalis group and quinidine sulfate (and allied cinchona alkaloids) can also depress the sinoatrial node in high degree. Vagal irritation by excessively sensitive carotid sinus by direct pressure of tumors by infec-

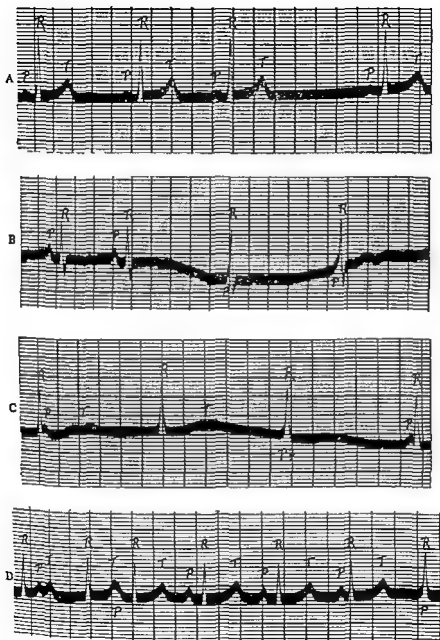


FIG 161 Electrocardiograms (Lead 2) showing (A) sinus arrhythmia and bradycardia or block (B) sinus arrhythmia with ventricular escape induced by deep breathing (C) atrioventricular dissociation due to independent action of sinoatrial and atrioventricular pacemakers at almost the same rate (50 per minute) and (D) atrioventricular dissociation due to escape of the atrioventricular nodal pacemaker at a rate of 90 per minute



tion in the neck or mediastinum and by intracranial tumors and high intracranial tension has likewise been reported as a cause of sinoatrial block. Sometimes the heart abruptly ceases to contract during anesthesia or surgical operations. Heart disease itself is a very rare cause of sinoatrial block but obstruction of blood supply to the sinoatrial node by atheroma or occlusion of its artery has been thought responsible in a few cases. Lesser degrees of bradycardia with rates of 45 to 55 are occasionally found in certain diseases such as epidemic parotitis and jaundice of either infectious or obstructive origin and sometimes during convalescence from any acute illness such as influenza.

The commonest of these conditions is simple sinoatrial slowing with regular heart action at rates of 30 to 40; less often there is gross sinus arrhythmia at these rates; the dropped beat is rare and least common of all is complete atrial standstill.

Both sexes and all ages are subject to these disorders of the sinoatrial mechanism but they are more common in youth. It was once thought that well marked sinus arrhythmia was a sign of a healthy heart; this is not so but it is true that in the absence of some special cause like a digitalis effect it is found more often in youth than in old age and it is abolished by the sympathetic stimulation that comes with infection for example rheumatic infection. To this extent then sinus arrhythmia is a sign of a healthy heart in that heart disease is less common in youth than in old age and less common in young persons without active infection than in those with such infection especially in a rheumatic environment. There is one exception to these remarks for infrequently in elderly persons with arteriosclerosis or heart disease a considerable degree of sinus arrhythmia may be found as a distinctly abnormal sign (Faulkner 1930).

**Symptoms.** There are no particular symptoms of sinoatrial bradycardia. If the rate is very slow or irregular there may be disagreeable palpitation or even weakness, dizziness and syncope when the periods of standstill are prolonged. In fact the marked slowing of the pulse with syncope and convulsions that may rarely result from extreme sinoatrial nodal depression is indistinguishable from the Morgagni-Adams-Stokes syndrome found with atrioventricular block unless graphic records are taken. Symptoms of congestive failure are rare. Nervous symptoms are common for the subjects of sinoatrial nodal depression may also have neurocirculatory asthenia.

**Signs.** The one sign of sinoatrial depression is the slow heart rate originating in the atria (Figure 161A, page 927). There may or may not be arrhythmia but it is rarely absolute so that there is little likelihood of confusion between atrial fibrillation with atrioventricular block and sinoatrial depression. When there is doubt an exercise test will make the pulse more regular in the case of sinoatrial arrhythmia and bradycardia with increase in rate while the pulse in atrial fibrillation will become more irregular. There may or may not be signs of heart disease, heart failure or hypertension. Roentgen ray study is of little or no value. Electrocardiography affords the greatest aid for it usually reveals

at a glance the abnormal mechanism and the relationship of atrial and ventricular activities (Figure 161)

At times in sinoatrial bradycardia the electrocardiogram shows that there is not always a normal atrioventricular sequence. The atrial rate may be so slow that the idioventricular pacemaker in the atrioventricular node does not wait for the impulse from the sinoatrial node but escapes. Such ventricular escape may be for one beat only or it may be for a group of beats (Figures 161B C and D page 927) or if the atria are wholly paralyzed it may constitute the entire cardiac mechanism (Figure 162). Ventricular escape is of no particular clinical significance but it constitutes an interesting physiologic adjustment of the body in case of need. It sometimes has been confused with heart block and so labeled wrongly; it is to be sure atrioventricular dissociation but it is not atrioventricular block. It has sometimes been called *interference dissociation* when both nodes are active without true heart block (Figure 161D).

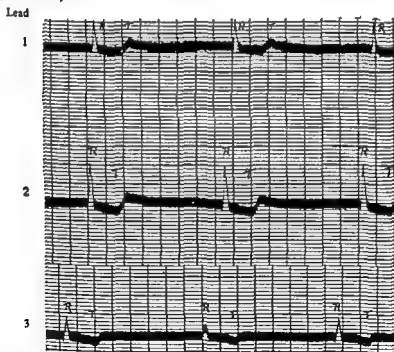


FIG 162 Electrocardiogram showing atrial standstill. No evidence of P waves in any of the three leads. Digitalis inversion of ST segments and T waves. A jugular phlebogram also failed to show any evidence of atrial activity in this case.

The course, complications, and prognosis of disturbances of sinoatrial rhythm due to depression are generally of little clinical importance. As a rule the condition is a transient anomaly, perhaps surprising and sometimes disagreeable but only rarely dangerous. In extreme cases there may be syncope and even death due probably to paralysis of the ventricular pacemaker also.

as with poisoning by quinidine or digitalis and with sudden standstill of the heart during anesthesia and surgical operations

The treatment consists of the omission of the toxic agent for example digitalis or quinidine or of the control of other underlying cause such as cerebral disease For marked bradycardia with faintness or syncope drugs may be needed atropine sulfate 1 mg (1/60 gr) or more subcutaneously every four hours as needed if vagal stimulation is the chief factor, otherwise epinephrine (adrenaline) or ephedrine Epinephrine hydrochloride may be given subcutaneously intravenously or even into or over the heart directly to stimulate a resumption of normal beating Life has apparently been saved in a number of cases by the intracardiac injection of 0.5 cc or less of a 1:1000 solution of epinephrine hydrochloride after the heart has stopped beating during anesthesia and surgical operations or obstetric procedures or in smaller dosage (0.1 cc) in stillborn infants This is an emergency treatment which should always be borne in mind and although it may often prove fruitless an occasional rescue makes it of decided value Cardiac massage when possible is however much more effective and wiser than the use of drugs and steps should more often be taken to carry it out to save lives otherwise doomed artificial respiration should be carried on simultaneously If serious heart disease is back of the cardiac standstill resuscitation by any method is very unlikely to succeed cardiac massage and electric shocks plus artificial respiration may conceivably be successful even in such cases but the difficulties of carrying out this therapy are almost always insurmountable

Ephedrine hydrochloride may be given in the dosage of  $\frac{1}{4}$  to  $\frac{1}{2}$  gr (15 to 30 mg) by mouth three or four times a day instead of epinephrine as prophylaxis against cardiac standstill but it is much less likely to be effective the same statement applies in general though to a lesser degree to the more recently introduced Paredrine given in the dosage of 40 to 60 mg by mouth three times daily (Nathanson et al 1942)

If an excessive sensitiveness of the carotid sinus on either side is found as a basis for syncopal attacks a cure can be effected by carotid denervation but it is very important first to rule out atrioventricular block revealed or increased by the effect of a normal carotid sinus reflex

For lesser grades of sinoatrial bradycardia block and arrhythmia no treatment at all is necessary The importance of the condition is often overemphasized and reassurance is more needed than anything else with discontinuance of various unnecessary remedies At times the most useful of all measures is electrocardiography to establish the diagnosis of an unimportant sinus arrhythmia or bradycardia and to rule out atrioventricular block which perhaps had been suspected as an aftermath of some serious infection such as influenza or pneumonia Almost invariably the supposed heart block present during convalescence from some important infectious disease proves to be merely sinoatrial bradycardia

*Intra atrial block* that is defective conduction of the wave of excitation and contraction through the atrial muscle itself has been produced and studied

in experimental animals it may be caused by certain poisons, such as quinidine sulfate and digitalis and by vagal stimulation. When of high degree the excitation wave may be so diverted as to alter the shape of the *P* wave of the electrocardiogram. Its existence in man has been indicated by variations in shape and rhythm of the atrial waves of the electrocardiogram for example during quinidine therapy but its clinical importance has not been established except in atrial flutter and atrial fibrillation.

*Interatrial block* partial and complete has been produced and studied in experimental animals but its occurrence in man although suggested and described has not been conclusively proved. To effect independent action of the two atria very extensive structural or functional changes would be necessary to block off all the extensive muscle tracts joining the two atria.

### ATRIOVENTRICULAR NODAL RHYTHM

A rare but interesting abnormal heart rhythm in man is that which originates in the atrioventricular node in the junctional tissues and controls both atrial and ventricular contractions. Atrioventricular nodal rhythm differs from ventricular escape and idioventricular rhythm only in that the atria as well as the ventricles are controlled by this lower pacemaker the sinoatrial node or other atrial pacemaker being superseded at least for the time being. The obstinacy of the atrium in maintaining its own pacemaker accounts for the great rarity of atrioventricular nodal rhythm. Occasionally unusual irritation or irritability of the junctional tissues accounts for premature beats or paroxysmal tachycardia of atrioventricular nodal origin but a steady rhythm at a slow rate arising from the junctional tissues is another matter and it is this that is called atrioventricular nodal rhythm (Figure 163 page 932).

Three conditions are necessary for the establishment even for a short time of atrioventricular nodal rhythm: (1) marked depression of the normal pacemaker of the heart situated in the sinoatrial node and failure of any other part of the atrial muscle to assume its role; (2) normal activity (potential or latent ordinarily) of the pacemaking function of the atrioventricular node; and (3) ability of the impulse to pass backward from the junctional tissue into the atria to cause their contraction that is an absence of a state of reversed block. The rate of impulse formation in the atrioventricular node averages in man about 40 per minute with a range of 30 to 50 and that heart rate therefore is usual in atrioventricular nodal rhythm. The heart action is as a rule quite regular sometimes absolutely so but at times there is more or less irregularity as in the case of sinus arrhythmia due to vagus and sympathetic nerve action on the junctional tissues. It is at times possible by vagal stimulation or through the action of digitalis to depress the reversed conduction to the atria and so to delay the ventriculoatrial interval and even block off the atrial response altogether that there may be atrial standstill with persistence of ventricular action (idioventricular rhythm) (Figure 162 page 929). Release of vagal inhibition by atropine or sympathetic stimulation by exercise

may first shorten the ventriculoatrial conduction time and then restore sinoatrial nodal function and normal heart rhythm

Atrioventricular nodal rhythm is a rare clinical condition it is unimportant except that it should be differentiated from the more serious disturbance of heart block It can be studied satisfactorily only by electrocardiogram although a phlebogram from the jugular pulse may indicate its presence Inspection of the jugular pulse (without a tracing) and fluoroscopic observation of the superior vena cava may show a very prominent pulsation due to coincidence of atrial and ventricular contractions suggesting this unusual rhythm but confirmation by electrocardiogram is necessary Any uniformly regular pulse at a rate of 35 to 40 per minute should be investigated to learn whether it is due to atrioventricular block (most likely) to sinus bradycardia (less

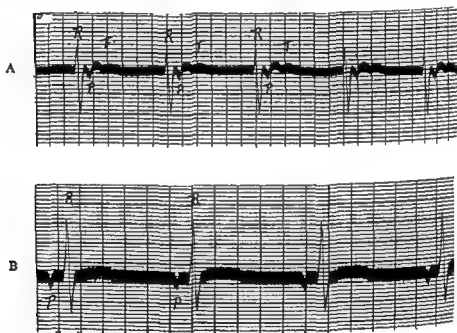


FIG 163 Electrocardiograms (Lead 2) showing atrioventricular nodal rhythm Two types (A) with P wave following the QRS wave and (B) with the P wave preceding the QRS wave

likely) or to atrioventricular rhythm (rare) As a rule in atrioventricular nodal rhythm the atrial contraction follows the ventricular contraction less often it coincides exactly with it and very infrequently precedes it (Figure 162) The P wave in the electrocardiogram is usually inverted and found at an interval of 0.1 to 0.2 second after the onset of the QRS wave it has been described as upright in rare cases due to an unusual position of the atria or unusual course of the excitation wave in the atria in relation to the axis of Lead 2 of the electrocardiogram If the atrial contraction follows the ventricular by a considerable interval usually over 0.2 second a second ventricular

contraction may in turn follow the atrial contraction producing a bigeminal heart action with one atrial contraction between two ventricular beats. This is a rare phenomenon that has been noted in a few cases.

Unusual sinoatrial nodal depression from the effect of digitalis or other cause generally unknown has been responsible for the occasional cases of atrioventricular nodal rhythm seen clinically. The diagnosis usually an unexpected one has been made by electrocardiogram. The condition is generally temporary or recurrent lasting for a few beats, minutes or hours at a time and alternating with normal rhythm; rarely it lasts for weeks or months or as a recurring condition for years. There may or may not be heart disease associated with it; usually there is not. The prognosis is dependent on other findings and not on the atrioventricular nodal rhythm which appears to be a harmless condition not needing treatment in itself and not easily controlled by any special therapy.

### ATRIOVENTRICULAR BLOCK

Depression of the function of conduction of the atrioventricular node (of Tawara) and bundle (of His) which join atrial and ventricular muscle results in delay or obstruction of the excitation wave as it travels downward from the atria to stimulate the ventricles. This delay in conduction has been called atrioventricular block. In early days it was known simply as *heart block* for it was the first kind of block to be recognized, being described long before the special tissue itself was discovered.

**Incidence.** Atrioventricular block is undoubtedly more common than statistics show for slight grades are easily and probably usually missed inasmuch as electrocardiograms are taken of relatively few patients. The higher grades of atrioventricular block are however certainly far less common than are premature beats, atrial paroxysmal tachycardia and atrial fibrillation; they are more common than atrial flutter and ventricular paroxysmal tachycardia. In the fifteen years from 1916 to 1930 inclusive at the Massachusetts General Hospital in an electrocardiographic series of 10 000 patients with cardiac symptoms or signs atrioventricular block was diagnosed in 641 cases (6.4 per cent). The block was complete in 79 or 12 per cent of these 641 cases and partial in 562 or 88 per cent (296 of the 562 cases of partial block showed only a delayed P-R interval). In another series of 69 cases of atrioventricular block coronary disease was apparently responsible in 35 (50.7 per cent), rheumatic infection in 19 (27.5 per cent), congenital defect in 1, syphilitic involvement in 1, digitalis medication in 9 and an unknown factor (probably congenital) in 4 cases (White and Jones, 1928). In another series of 74 cases a congenital etiology was diagnosed in 14 per cent, rheumatic heart disease in 4 per cent, syphilis in 7 per cent and other myocardial disease probably coronary in type in 75 per cent (Campbell, 1944).

**Mechanism (abnormal physiology).** Atrioventricular block or defective atrioventricular conduction is due to the failure of the atrioventricular node

and bundle to transmit the excitation wave at a normal rate from atria to ventricles because of destruction from disease or because of prolongation of the refractory period resulting from disease faulty nutrition vagus nerve action or fatigue from excessive speed of stimulation as in extreme tachycardia Atrioventricular block is a more or less normal phenomenon in atrial fibrillation atrial flutter and very rapid atrial paroxysmal tachycardia when the atrial rate is so fast over 200 and often over 300 per minute that even perfectly normal atrioventricular junctional tissue cannot resume a responsive state between successive stimuli in such cases 2 to 1 or higher grades of block quite naturally are found In these patients such block is of no serious significance in fact it is actually helpful for the heart and circulation Treatment of atrial fibrillation and atrial flutter consists chiefly of attempts to increase the grade of block in order to reduce the ventricular rate

When however at normal or only moderately accelerated speed of atrial activity there is delay or obstruction to the passage of the impulse to the ventricles an important type of atrioventricular block exists Although the block may originate in any part of the short tract of junctional tissue between the atrial muscle and the bifurcation of the bundle into its two branches which pass to right and left ventricles respectively and even in these branches themselves if both are affected the most susceptible and probably one of the commonest sites of blocking is at the very point where atrial muscle enters the junctional tract this has been shown by animal experiments and clinical observations (Lewis White and Meakins 1914 White 1915) It appears likely that toxic and nervous influences act chiefly at this point although destructive lesions are more common lower down that is in the bundle itself

Atrioventricular block may be temporary and functional or permanent and organic It may be of all grades from very slight delay in conduction so that the *P R* interval of the electrocardiogram measures 0.21 second to complete block when no impulses at all pass through from atria to ventricles Any defect in atrioventricular conduction short of complete dissociation is called partial heart block By far the commonest of all grades of block are the lesser ones with simple delay in conduction without dropped beats (Figure 164) cases with such slight block usually pass unrecognized unless graphic records are taken The *P R* interval in these cases varies from 0.21 up to 0.50 second or even longer but intervals of over 0.30 second are decidedly rare Faulkner has reported a case in which the *P R* intervals actually exceeded the *R R* intervals in duration (Faulkner 1935)

Occasional dropped beats and higher grades of partial block in which every fourth atrial impulse is blocked (called 4 to 3 block because there are four atrial contractions to three ventricular contractions), or every third impulse is blocked (3 to 2 block) or every second (2 to 1) or every second and third (3 to 1) are usually easily recognized clinically and can often be analyzed simply by careful auscultation of the heart and by inspection of the jugular pulse though more easily by electrocardiogram (Figure 164)

Grades of partial heart block higher than 2 to 1 are very rare although

3 to 1 (Figure 164C) 4 to 1 and even 5 and 6 to 1 do occur. As a rule the pacemaker in the atrioventricular node escapes and establishes an independent ventricular or idioventricular rhythm if the grade of block becomes greater than 2 to 1. Such a rhythm called complete heart block usually becomes established at ventricular rates of 35 or below, most commonly at about 30

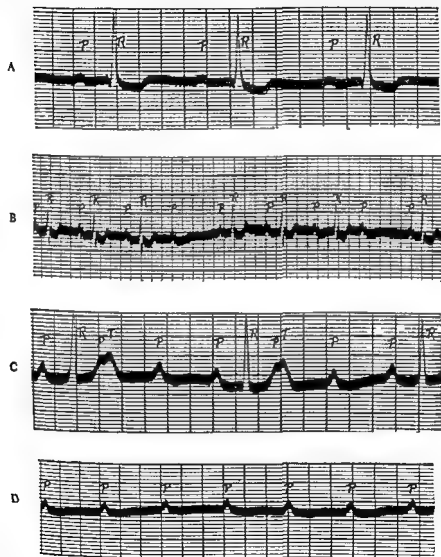


FIG 164 Electrocardiograms (Lead 2) of partial atrioventricular block (A) simple delay in conduction ( $PR$  interval = 0.32 second) (B) occasional dropped beats with varying  $PR$  intervals giving rise to the Wenckebach periods at the time of the dropped beats (unequal to the interval covering two usual beats) (C) three to one block and (D) entire absence of ventricular contractions during a Morgagni Adams Stokes attack. Time interval = 0.2 second



per minute but higher in infants and young children for example at about 50 per minute. Two to one atrioventricular block with an atrial rate at the normal average of 72 gives a ventricular rate of 36 which is but slightly higher than the usual rate in complete heart block. These observations are important for they help to explain the occasional transitions back and forth between partial heart block and so called complete heart block which transitions have been sometimes regarded as mysterious. Also they explain the rarity of long ventricular standstill and of the Morgagni Adams Stokes syndrome. The atrioventricular nodal pacemaker usually escapes to prevent this syndrome rarely is it unable to do so because it is itself depressed. Finally the observations noted above explain the occasional instances in supposedly complete heart block when an atrial impulse passes through the junction to give rise to a ventricular contraction. In other words complete heart block does not mean that impulses can never pass from atria to ventricles.

Rarely a state of double atrioventricular block exists in which there is not only complete dissociation between atria and ventricles but the idioventricular pacemaker itself may be blocked as in an early patient of my own whose electrocardiogram showed complete atrioventricular block and partial (2 to 1) idioventricular block (White 1918) and in a recent case of Langendorf and Katz (1942).

The ventricular rhythm in heart block of atrioventricular type may be regular or irregular. Usually it is regular, due to the fact that there is simply a uniform delay in conduction time without dropped beats. A regular 2 to 1 or 3 to 1 or complete block sequence also produces regular ventricular action but at slow rates of 40 to 20. When the ventricular action is irregular it is regularly irregular, for a dominant rhythm is maintained and in the arterial pulse equal spacing of large groups of beats against each other is possible but equal spacing may not be found if comparison of the arrhythmia with the regular beats is limited to the pause due to the dropping of a beat since the interval between the beats preceding and following a dropped beat may or may not be equal to the length of two normal cycles. It frequently is shorter because of the progressive delay that may occur in conduction (increasing *P R* intervals) up to the time of the dropped beat with marked shortening of the *P R* interval of the first beat after the pause due to recovery of the conducting tissue (Figure 164B page 935). This variation in conduction not only causes the pause in the arteriogram to be considerably shorter than the interval covered by two other cycles but it also results in some inequality in length of the 'normal' cycles (the pauses in heart block with dropped beats have sometimes been called Wenckebach's periods).

The atrial rate in a v block is usually regular but there may be any kind of atrial arrhythmia with any grade of block. An interesting form of atrial arrhythmia is occasionally found in complete heart block and consists of a temporary quickening of the *S A* rhythm or prematurity of normal atrial complexes in the electrocardiogram when they fall directly after the ventricular contractions quite possibly due to the stimulus to the *S A* node by the

vigorous ventricular contraction Sometimes also even in complete  $\pm$  v block retrograde atrial contractions occur Atrial fibrillation is a not very rare accompaniment of complete heart block and atrial flutter has also been noted

**Etiology Cause** Atrioventricular block is caused either by temporary toxic or functional conditions by permanent organic disease or by both factors acting together It is most commonly temporary and functional but this type is likely to be missed because it is so transient and usually so slight in degree Examples of temporary or functional causes of atrioventricular block are asphyxia excessive vagal stimulation digitalis poisoning quinidine poisoning the effect of other vegetable or mineral poisons uremia and the temporary effects of certain infectious diseases such as rheumatic fever and diphtheria from which recovery may take place without persistence of heart block

Permanent and organic block is the result most frequently of extensive coronary disease There may be at first simply a narrowing of the vessel or vessels supplying the junctional tissues with blood with temporary or slight atrioventricular block which varies with the activity of the subject and with the state of the circulation With greater narrowing of the coronary vessels and limitation of blood supply the block becomes more permanent and greater in degree although the junctional tissue itself may show astonishingly little pathologic change Finally with great or complete arterial occlusion and obstruction to the blood supply the block may become complete and there may or may not prove to be extensive or complete degeneration and fibrosis of the atrioventricular bundle and node (actually a small infarct) An interesting occasional cause of paroxysmal a v block lasting for a few hours or a few days accompanying infarction of the posterior wall of the left ventricle is acute occlusion by thrombosis of the right coronary artery or of the circumflex branch of the left whence is derived the major part of the blood supply to the a v junctional tissues in almost all individuals Other less commonly acquired but important causes of permanent and organic block are virus diseases like epidemic parotitis (mumps) which have been more often recognized as factors in recent years syphilis acting directly by infection of the bundle of His or more often by pressure from adjacent gummata destructive lesions following diphtheria in rare cases the results of rheumatic inflammation invasion of the junctional tissue by the vegetative lesions of bacterial endocarditis and very rare causes like pressure from neoplasms and cysts miliary tuberculosis and trauma Finally atrioventricular block may be of congenital origin in rare cases associated with interventricular septal defects and abnormal course or development of the junctional tissues congenital block may be partial or complete

**Sex** The male sex shows permanent heart block twice as often as does the female probably because of the higher incidence of serious coronary disease in males but both sexes are about equally affected by temporary or functional block

**Age** Atrioventricular block is much more common in older persons because of their greater incidence of serious coronary disease About 90 per cent of

the higher grades of permanent heart block occur after the age of fifty years

**Pathology** No lesion at all may be found in the junctional tissues when there is transient or functional atrioventricular block rarely there may be no obvious lesion even with more or less permanent block of high grade On the other hand there may be considerable inflammation degeneration or fibrosis of the atrioventricular bundle and node without heart block Thus there is by no means a close correlation between the degree of atrioventricular block and the condition of the atrioventricular junctional tissues partly because of the fact that heart block is essentially a functional disturbance not necessarily dependent on obvious disease partly because the damage may be more in the coronary vessel or vessels supplying the node and bundle than in the node and bundle themselves and these vessels are not always carefully studied and partly because a small amount of tissue may be able to carry on normal function in spite of much damage or destruction of the bundle as a whole It is true however that permanent atrioventricular block of high degree is usually associated with extensive pathologic changes in the junctional tissue (inflammation degeneration or fibrosis) It is important in the postmortem study of the heart of a patient with atrioventricular block to examine the coronary vessels supplying the junctional tissues for narrowing or occlusion as well as to study the conducting tissues itself

Fibrosis of the bundle of His from coronary arteriosclerosis is the lesion most commonly found in heart block infiltration by rheumatic syphilitic or other infectious process like bacterial endocarditis and calcareous extension from the region of mitral or aortic valve which is calcified at its base is occasionally encountered while congenital defects of the bundle are rare As time passes we have become aware that now and then infectious diseases of childhood and youth may result in scarring of the junctional tissue which, quite symptomless may be wrongly ascribed to congenital or coronary etiology

It is of more than passing interest that atrioventricular block is an uncommon complication of massive coronary thrombosis with myocardial infarction diagnosable clinically while relatively few cases of atrioventricular block have had a history of acute clinical myocardial infarction The answer lies in the fact that occlusion of some of the larger coronary vessels may occur with serious heart damage but escape of the particular part of the heart in which lie the node of Tawara and bundle of His while a localized occlusion of the small vessels supplying these specialized structures creates too slight a clinical disturbance to be recognized in most cases the seriousness of the two conditions as evidence of important coronary heart disease is however much the same Of a series of 328 cases of clinical myocardial infarction analyzed only 3.6 per cent had atrioventricular block while of 117 patients with atrioventricular block only 11.9 per cent had had a history of myocardial infarction the frequency of angina pectoris was even less there having been but 1.5 per cent of cases of atrioventricular block among 700 patients with angina pectoris without clinical myocardial infarction and 9.4 per cent of cases of

angina pectoris without myocardial infarction among the 117 patients with atrioventricular block (Salcedo and White 1935)

Symptoms Atrioventricular block rarely causes any symptoms since it is usually of slight degree even block of high degree with dropped beats or very slow pulse may remain unnoticed by the patient Sometimes however there is complaint of a disagreeable palpitation due either to the pause in the heart's action when the atrial impulse is blocked to the forceful thump following the pause or to the constant pounding when the heart beats very slowly (about 30 per minute) The sensitiveness of the patient rather than the irregularity or slowness of the pulse determines the presence or absence of symptoms Pain and dyspnea are not common they are the result of complicating angina pectoris congestive heart failure or neurocirculatory asthenia

Much has been written in the past about the *Morgagni Adams Stokes* syndrome perhaps too much in view of its rarity Nevertheless it is an important complication of atrioventricular block when it does appear This syndrome as originally described consists in the association of syncope and epileptiform convulsions with marked slowing of the heart's action (Morgagni 1760 Adams 1827 Stokes 1846) but all grades of disturbance of the cerebral circulation may exist from slight dizziness and faintness with transient ventricular standstill of two or three seconds duration up to extreme degrees of the syndrome with cessation of the heartbeat for as long as twenty or thirty seconds (Figure 164D page 935) The patient with these distressing symptoms may have warning and find time to sit or to lie down or he may fall to the ground suddenly while standing or walking The clinical condition is similar to the result of the cerebral anemia occurring in some cases of extreme tachycardia or of atrial depression with standstill of atria as well as ventricles but the mechanism is of course quite different and the prognosis and treatment not the same It is better not to lump all these conditions into this one heading as has been somewhat the custom An electrocardiogram should be secured between attacks to see whether or not some degree of atrioventricular block is present As a rule sudden ventricular standstill due to atrioventricular block does not happen without at least some delay in conduction at other times rarely paroxysmal atrioventricular block does occur but graphic records are necessary for its proof

Signs The pathognomonic sign of atrioventricular block is either (1) delay in the interval between the atrial and the ventricular pressure waves in the venous pulse (*a-c* interval) beyond the normal usually put at 0.2 second or between the atrial and the ventricular electric waves in the electrocardiogram (*P-R* interval) beyond the normal the upper limit of which is routinely placed at 0.2 second and with or without dropped beats (rare to many) (Figure 164 page 935) or (2) complete dissociation between atrial and ventricular rhythms with slow ventricular rate

A *P-R* interval of 0.2 second is traditionally the upper limit of normal but such a measurement must be analyzed with care in every case The range of normal is wide in this particular as in many others (see Chapter 2) In infants

the normal varies from 0.08 to 0.14 second in children from 0.10 to 0.18 second and in adults from 0.12 to 0.22 second. Thus 0.20 second would be well within the normal for one adult and prolonged for another whose average should be perhaps 0.15 second. One must use considerable judgment and sometimes secure serial records over long intervals of time for sure appraisal of variations of atrioventricular conduction time unless they are grossly abnormal.

With training and experience it is often possible to analyze the jugular venous pulse by inspection and to observe well marked delay in the interval between atrial and ventricular waves or to see completely blocked atrial waves falling in longer ventricular pauses. The difficulty or impossibility of noting slight changes, however, and the likelihood of confusion even after training make graphic records—preferably electrocardiograms—essential for the establishment of the diagnosis of atrioventricular block in all but the most marked cases in which there happen to be actual dropped beats or very slow pulse rates (35 or less per minute). The phlebogram by measurement and the electrocardiogram at a glance show the presence and grade of block (Figures 36 page 167 and 164 page 935). Mechanical pulse tracings taken from cardiac apex or arm artery may rarely show the atrial pressure waves and the presence of block (Figure 31 page 158), but the chief value of the analysis of the ventricular action in arteriogram or cardiogram in heart block is in the finding of a dominant rhythm when there are dropped beats. Without auscultation, however, this finding does not tell whether the pause is due to a true dropped beat or to a ventricular premature beat that has failed to show itself in the arterial pulse. Moreover, the varying conduction time that often occurs before and after a dropped beat shortens the pause and may be confusing in measurements of the arteriogram.

Auscultation in atrioventricular block may sometimes reveal an extra sound usually faintly heard and often double due to the atrial contraction which may be separated sufficiently from the ventricular contraction to be clearly heard in a few cases. This additional sound may come just before the normal first heart sound making the latter seem reduplicated or it may come well before it and if the heart rate is fast give rise to a presystolic gallop rhythm. If there is considerable delay in conduction the extra sound may come in the middle of diastole early in diastole or immediately after the normal second heart sound giving rise respectively if the heart action is fast to middiastolic gallop rhythm protodiastolic gallop rhythm, or simple reduplication of the second sound (Chapter 5). Finally in heart block of high degree with dropped beats or in complete atrioventricular block the atrial contractions may be heard usually dimly at regular intervals between the ventricular contractions or they may at times coincide with the ventricular contractions causing an accentuation of the first second or third sound (Figures 13 and 14 in Chapter 5).

The heart rate in atrioventricular block is as a rule normal because there are generally no dropped beats and the atrial rate is unaffected. With dropped

beats showing a higher grade of block the ventricular and peripheral pulse rates fall and tend at first to be irregular. With 2 to 1 and complete heart block the heart rate falls to 40-30 and rarely somewhat lower. Very marked slowing of the pulse down to 20-10 or even 2 or 3 beats a minute is rare and always very transient. It is due to depression of the idioventricular pacemaker which does not take up the control of the heart when the atrial impulses are almost completely blocked off from the ventricles or else it is due to this same ventricular pacemaker depression coming on periodically in the course of complete heart block. It is most common in the transitional stage between partial atrioventricular block of high grade and complete block before the idioventricular rhythm has become established. When complete heart block is well established excessive slowing of the heartbeat though possible is rare. It is the ventricular standstill with cerebral anemia occurring with this extreme slowing of the heart rate that is responsible for the syncopal attacks in the Morgagni-Adams-Stokes syndrome. The slowest heart rate that has been recorded is one beat a minute (Odnozola 1920) but ventricular standstill of from 2 to 3 minutes with recovery has been reported also of course this must necessarily be a transient condition if it is more prolonged or often repeated death results. The longest period of ventricular standstill proved electrocardiographically has been so far as I know 79 seconds following a period of over 3 minutes of abnormal ventricular tachycardia including ventricular fibrillation in this patient no pulse or cardiac contraction could be seen felt or heard for a period of 5 minutes recovery with two months more of life followed an injection of epinephrine directly into the heart (Levine and Matton 1926). The more recent notable case of a twenty minute cardiac arrest with complete recovery after cardiac massage apparently involved the whole heart (Adams and Hand 1942).

The reaction of the heart rate to various factors in the presence of atrioventricular block is of interest. Often with lesser grades it increases normally with exercise and excitement but often even with lesser grades the reverse happens and the heart slows. This paradoxical condition is due to the increase in the grade of block and number of dropped beats as a result of the increase in atrial rate the conducting tissue is no longer able to carry every impulse at the increased atrial rate so that 2 to 1 block develops with marked slowing of the ventricular rate while there is simply delayed conduction at only a moderately slow heart rate. For example at rest both atrial and ventricular rates may be the same 72 per minute while on exercise the atrial rate may rise to 96 and the ventricular rate fall to 48 (2 to 1 block). The variation in atrial rate dependent on respiration may also in a critical case have a similar effect (Bourne 1928) this is particularly true in the case of Cheyne-Stokes respiration. Vagal stimulation by carotid sinus pressure and also the administration of digitalis may easily convert a slight grade of atrioventricular block into a high grade though rarely if ever complete.

The blood pressure is unaffected in heart block unless the ventricular rate is very slow (about 30 per minute) when there tends to be a rather high

systolic pressure (150 to 160 mm) and a full pulse pressure (from 80 to 100 mm) this is a more or less compensatory condition and is due to increased filling of the heart during the prolonged diastole together with full emptying during the prolonged systole that always accompanies a slow pulse rate. Considerable hypertension however in a case with complete heart block is always a complication and never a part of the circulatory mechanism of complete heart block itself.

The blood flow at rest in atrioventricular block is not remarkable even at very slow heart rates because with a slow pulse the output of the heart per beat is almost correspondingly increased. An output of 120 cc of blood per beat at a heart rate of 35 per minute gives a minute volume of blood flow of 4.2 liters not much less than that of the normal 4.9 liters at a heart rate of 70 and an output of 70 cc per beat. With complete heart block however and to a less extent with partial block of high degree there is relatively little variation of the blood flow possible with exercise on account of the inability of the heart to increase its rate and because the ventricles are already putting out almost their maximum capacity per beat.

Roentgen ray studies are of little or no help in the analysis of atrioventricular block although it is frequently possible to observe fluoroscopically the independent atrial and ventricular actions and when the ventricular rate is very slow to note the increased fullness of cardiac contraction with enlargement which may be entirely due to the increased diastolic filling.

Electrocardiography is the only satisfactory method for the analysis of this disturbance of rhythm (Figure 164 page 935) it has also the great advantage of giving other evidence especially T wave changes of any very extensive or rapidly progressive coronary heart disease.

There may or may not be signs of cardiac enlargement and failure valvular disease and hypertension. Usually there are cardiac signs of some sort especially enlargement with the greater degrees of atrioventricular block.

**Course and prognosis.** Atrioventricular block is always important not so often in itself as in showing the existence of serious disease or toxic states. This disturbance of rhythm is usually an incidental or accidental discovery in the course of routine health examinations or during the study of some illness cardiac or noncardiac. It is discovered only very rarely at the time of its origin. The only sign of its presence may be electrocardiographic or there may be the extreme signs and symptoms of block of high degree with the Morgagni-Adams-Stokes syndrome.

In young persons not acutely ill with rheumatic or other infection the finding of atrioventricular block even of highest grades is compatible with good health and full activity for many years and even for long lives this seems to be particularly true of instances of congenital heart block that survive early childhood. Even pregnancy has been normally carried through in cases of complete heart block with good reserve and little or no other evidence of heart disease. In older persons new heart block is more serious even in slight grades unless digitalis is responsible for coronary disease of progressive character is

likely to be the cause and sometimes angina pectoris is associated with it. When the heart block appears in the course of an acute infection at any age it adds somewhat to the gravity of the prognosis for it may mean serious cardiac involvement. Rarely atrioventricular block may itself kill as the result of ventricular standstill. Such a fate is usually ushered in by attacks of syncope the Morgagni Adams Stokes syndrome but this syndrome does not always end fatally it may occasionally be a temporary condition with complete recovery following the establishment of a stable complete heart block or very uncommonly a return to normal rhythm to be followed by normal activity and years of life.

**Complications** The only important complications of atrioventricular block are gross myocardial infarction angina pectoris congestive heart failure the Morgagni Adams Stokes syndrome and intraventricular block the last named will be discussed later in the present chapter. Congenital interventricular septal defects are the rule in the very rare cases of congenital heart block.

**Treatment** Atrioventricular block rarely needs any treatment for itself but it frequently is associated with or due to some disease which does demand treatment especially rheumatic infection syphilis and coronary heart disease with myocardial infarction or angina pectoris. Improvement of these conditions spontaneously or with the help of more or less specific therapy may be attended by a decrease or disappearance of the heart block. A few striking cases of lessening of heart block in syphilis following specific therapy have been reported probably due to the clearing up of a gumma pressing on the atrioventricular junctional tissue or of an inflammatory condition of the tissues themselves. Full salicylate therapy has been said to have reduced acute rheumatic heart block and the new hormone therapy with ACTH or cortisone is very encouraging (see Chapter 14). Rest and other treatment of angina pectoris have at times been followed by decrease in coincident heart block. The high grade heart block that may appear paroxysmally for a few hours or a few days at the onset of myocardial infarction usually of the posterior wall of the left ventricle secondary to acute occlusion of the right coronary artery or of the circumflex branch of the left tends to clear up spontaneously without special therapy other than complete rest but its amelioration can be effected on occasion by the use of the nitrites especially erythrol tetranitrate 0.015 to 0.03 gm ( $\frac{1}{4}$  to  $\frac{1}{2}$  gr) every three or four hours. Ample antitoxin therapy of severe diphtheria has been associated with recovery after the appearance of atrioventricular block. Finally the treatment of congestive failure by digitalis in some cases complicated by atrioventricular block has even resulted in the reduction of the grade of block along with general improvement in spite of the fact that digitalis itself is sometimes alone responsible for heart block.

If certain toxic agents like quinine and digitalis are the cause of a serious grade of heart block they should be at once omitted if they produce but slight grades of block they may be discontinued or else reduced in amount careful watch being established that the block be not increased.

In the presence of atrioventricular block not produced by some poison that



can be controlled some attention to the future health of the affected individual should be given even though there be no symptoms produced by the block or any evident heart disease. Care should be exercised to avoid extreme fatigue overexertion and infections but otherwise there should be no restrictions or therapy, unless particularly indicated. The finding of heart block especially in a young person needs in no way to render him a cripple but electrocardiograms and physical examination at intervals perhaps once every year or two are useful guides to the progress favorable or unfavorable of the state of the heart.

Finally in rare instances it is necessary to treat the heart block itself when ventricular standstill is so frequent or of such long duration that cerebral symptoms develop dizziness faintness syncope and convulsions (Morgagni Adams Stokes syndrome). The most that can be done as a rule is to give therapy to prevent the attacks rarely an attack itself can be treated if it is of long duration and facilities are at hand. The most effective measure in the prevention of the Morgagni Adams Stokes syndrome is the subcutaneous or intramuscular injection of *epinephrine (adrenaline) hydrochloride* 0.25 to 1 cc of the 1:1,000 solution (equaling 0.25 to 1 mg) at intervals of every few hours as needed (introduced by Hardoy and Houssay 1917 and by Phear and Parkinson 1922). Recently epinephrine in oil (2 mg of epinephrine hydrochloride in 1 cc of sesame or peanut oil) has been introduced in this prophylactic therapy with the advantage that because of its slow absorption under the skin only one or two injections may be needed in 24 hours when the effect is beginning to wear off. Massage of the site of injection will introduce some of the as yet unabsorbed epinephrine into the circulation. This is almost invariably effective in preventing ventricular standstill either by decreasing the grade of atrioventricular block or more commonly by stimulating the activity of the idioventricular pacemaker. The heart rate may be maintained above 30 per minute sometimes even as high as 50 for hours or days at a time by this therapy. The atrial rate is simultaneously raised by the epinephrine to 90 or 100 or more. Less effective immediately but more gradual and prolonged in its action and closely related in effect to epinephrine is *ephedrine* given in the dose of 15 to 30 mg ( $\frac{1}{4}$  to  $\frac{1}{2}$  gr) of the hydrochloride three to six times daily by mouth sometimes considerable nervousness results from its use. *Paredrine* a similar drug has also been used with favorable effect given in the dosage of 40 to 60 mg by mouth three times a day (Nathanson et al 1942). Very rarely even digitalis may be tried if it keeps the rate from rising to critical levels above which serious  $\text{A-V}$  block is set off. Finally three other drugs have been given thyroid extract or thyroxin barium chloride and atropine sulfate. Each of these drugs has sometimes succeeded but more often failed they are less effective than epinephrine and ephedrine and rarely worth bothering about.

For emergency treatment of a prolonged period of ventricular standstill with syncope convulsions and apparently impending death the intracardiac injection (by long needle) of 0.1 to 0.5 cc of 0.1 per cent solution of *epi-*

nephrine hydrochloride (i.e. 1:1000) may be tried (though usually unsuccessfully) provided ventricular fibrillation is not itself the cause of the asystole. Electrocardiographic evidence of previous attacks of the Morgagni-Adams-Stokes syndrome in the case in question is important. Epinephrine may be lifesaving if administered within a few minutes of the cessation of the heartbeat but the drug is not without danger since it can itself induce ventricular tachycardia and fibrillation (Hoff and Nahum 1934). Large dosage such as a full cc of 1:1000 epinephrine hydrochloride solution should for that reason be avoided.

**Differential diagnosis.** Atrioventricular block when there is simply delayed conduction can be differentiated with certainty from normal rhythm only by the electrocardiogram or by a good phlebogram. When there are dropped beats heart block is to be differentiated from premature beats which are very early or very faint. Careful auscultation usually permits a clear distinction between the two. Finally atrioventricular block of high degree must be distinguished from marked sinoatrial bradycardia or block which usually requires venous or electric tracings for diagnosis but which can at times be detected by trained observation of the jugular pulse. The Morgagni-Adams-Stokes syndrome is to be differentiated from other cause of syncope and convulsions usually an easy matter because of the very slow heart rate or actual cardiac standstill, the absence of paralysis, the absence of a previous history of epilepsy, nephritis, diabetes and neurocirculatory asthenia and the presence of other signs of heart disease besides the block itself. It is however important to note that high grade heart block may be wholly paroxysmal with normal P-R interval between the relatively short periods of bradycardia or syncope. Electrocardiograms or at least direct observation of the heart rate should always be secured during the actual attacks.

### INTRAVENTRICULAR (BUNDLE BRANCH) BLOCK

When there is depression of conduction in the branches of the atrioventricular bundle intraventricular or bundle branch block is said to exist. Undoubtedly much of this intraventricular block is unrecognizable because either it is slight in degree in the larger branches or it affects only a limited number of the smaller branches of the conducting system (Purkinje network, Purkinje 1845). When block exists to a moderate or marked degree in either of the two main bundle branches (right or left) or in a very extensive area of the finer network it becomes evident in the electrocardiogram but its presence cannot be proved in any other way. It is better to speak of lesser grades of intraventricular block of left bundle branch type or of right bundle branch type or of uncertain type (slight aberration) than to use the term arborization block for it is as yet impossible to distinguish partial bundle branch block of either main branch from extensive block of the lesser branches.

**Incidence.** As in the case with slight grades of atrioventricular block intraventricular block is undoubtedly more frequent than statistics generally indi-

cate since electrocardiograms are essential for its detection. Intraventricular block of all grades is somewhat more common than atrioventricular block of all grades. Of 10 000 cases electrocardiographed at the Massachusetts General Hospital during the fifteen years from 1916 to 1930 inclusive there were 734 cases of intraventricular block (7.3 per cent) and 641 cases of atrioventricular block (6.4 per cent). Of the cases of intraventricular block 223 showed full degrees or marked preponderance of left or of right bundle branch block and 511 lesser grades of block, the left bundle branch type was considerably more common than the right but not to the extent it was once thought to be before the introduction of the precordial leads or the recognition that a wide S wave in Lead I usually indicates a type or grade of right bundle branch block. During the decade from 1934 to 1943 inclusive there were at the Massachusetts General Hospital 1 040 cases of clear-cut bundle branch block of either branch type, 258 of which were right and 782 left.

**Mechanism (abnormal physiology)** Bundle branch block may be due as in the case of atrioventricular block either to temporary functional or to permanent organic conditions but temporary or functional bundle branch block is very rare compared to both permanent bundle branch block and functional or temporary atrioventricular block. Conduction when depressed in both main bundle branches equally may give rise to a condition that is indistinguishable from atrioventricular block but when one branch is more depressed than the other or some very extensive area of the finer arborizations is affected the lack of balance is shown in the electrocardiogram which simulates a dextrogram or a levogram. If the left bundle branch is diseased or depressed so that the impulse is delayed in reaching the left ventricle spreading to the ventricular muscle wholly or in large part by the right branch the condition is called left bundle branch block and the electrocardiogram has the character of a dextrogram (Figure 165) when the right bundle branch conduction is grossly defective the ventricular deflections of the electrocardiogram resemble the levogram and right bundle branch block is present (Figure 166). The nomenclature is that based on the convincing work and conclusions of Mann and of Wilson and his associates and of others in recent years in opposition to the older point of view now largely discarded with its opposite nomenclature of bundle branch block.

Wilson (1942) called attention to the reason for the earlier confusion based on the common dissimilarity of the curves of bundle branch block in man and in the dog. The crux of the situation lies in the universally median vertical position of the dog's heart in contrast to the commonly diagonal or horizontal position of man's heart. As Wilson says had direct or precordial leads been taken earlier the confusion need never have arisen.

Between the two extreme conditions of full left and full right bundle branch block there are various grades and combinations of intraventricular block sometimes difficult accurately to analyze. Intraventricular block is frequently found present when there are high degrees of atrioventricular block.

The criterion for the diagnosis of bundle branch block is an abnormal

width or duration of the first ventricular complex that in the *QRS* wave provided the *PR* interval is not too short (that is not so little as 0.1 second or less). An upper limit of 0.1 second has been more or less routinely regarded as the borderline beyond which bundle branch block is to be diagnosed but it is undoubtedly true that on occasion the normal may exceed that slightly

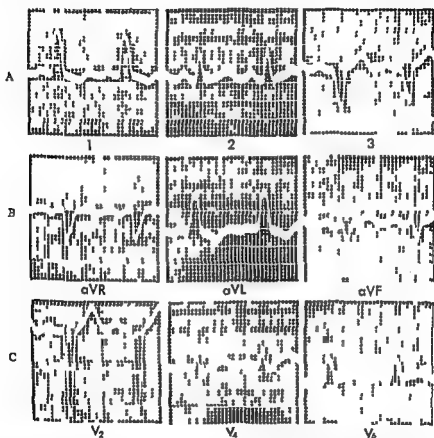


FIG 165 Electrocardiogram in left bundle branch block female age 68 (A) Bipolar limb leads 1 2 and 3 (B) unipolar limb leads *aVR* *aVL* and *aVF* (C) three precordial leads *V*<sub>1</sub> *V*<sub>4</sub> and *V*<sub>6</sub>. Note the wide *QRS* waves throughout the left axis deviation in the limb leads and especially the notched and sturred *R* waves in Leads *V*<sub>1</sub> and *V*<sub>4</sub>. Time = 0.04 and 0.20 second amplitude 1 mm = 0.10 mv

(up to 0.11 second or even a shade more) and also that very large hearts (dilated hypertrophied or both) can have widened *QRS* waves (up to 0.12 second) without actual bundle branch block. It is of some related interest that the very large heart of the normal elephant has a wide *QRS* wave of about 0.2 second and that the human infant's heart records a *QRS* wave of only 0.05 second. Thus as in the case of the *PR* interval so too in judgment concerning the *QRS* wave much care must be used with full recognition of the

wide range of the normal heart (see Chapter 2), the electrocardiographic time intervals are to a certain extent at least a function of heart size

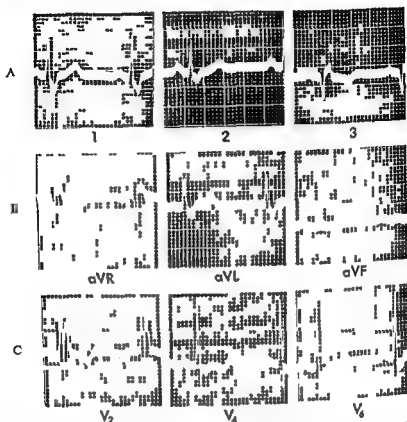


FIG 166 Electrocardiogram in right bundle branch block male age 60 (A) Bipolar limb leads 1 2 and 3 (B) unipolar limb leads aVR aVL and aVF (C) three precordial leads V<sub>2</sub> V<sub>4</sub> and V<sub>6</sub> Note the wide Q waves in Leads 1 2 aVL and V<sub>6</sub> the wide R waves in Leads 3 and aVR and especially the wide M shaped R waves in Lead V<sub>2</sub> Time = 0.04 and 0.20 second amplitude 1 mm = 0.10 mv

There may occur as in the case of most other disturbances of rhythm and conduction paroxysmal bundle branch block such a mechanism which may antedate by weeks or months a permanent change. An interesting variation is 2 to 1 bundle branch block (see Figure 167)

**Etiology Cause** The commonest cause of bundle branch block is coronary atherosclerosis resulting in faulty nutrition degeneration and eventual fibrosis of the larger or smaller bundle branches. Occlusion of a large coronary artery (more often the right or the circumflex branch of the left) or of the smaller vessels which supply the bundle branches may be followed by infarction involving right or left main trunks or lesser branches.

There is a considerable discrepancy however between the occurrence of bundle branch block and the clinical evidence of coronary heart disease although less than in the case of atrioventricular block. In a series of 700 pa-

tients with angina pectoris without myocardial infarction there were 7.7 per cent who showed intraventricular block (as compared to 1.5 per cent who showed atrioventricular block) while among 328 cases of myocardial in

Lead

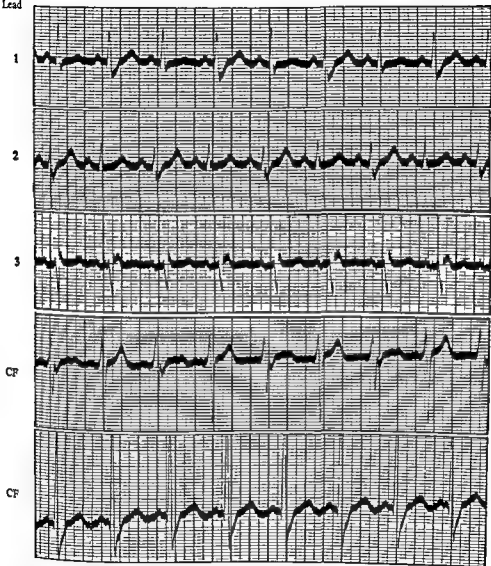


FIG 167 Alternating right bundle branch block in a man age 59. The alternation has cleared in Lead CF in which lead there is constant right bundle branch block. Time = 0.10 and 0.20 second amplitude 1 mm = 0.10 mv.

farction there were 9.5 per cent with intraventricular block (4.2 per cent had atrioventricular block) on the other hand among 181 cases of bundle branch block of all grades 39.1 per cent showed angina pectoris without myo

cardial infarction (29.8 per cent) or myocardial infarction with or without angina pectoris (9.3 per cent) (Salcedo and White 1935)

Other less common causes of organic intraventricular block are scarring from rheumatic myocarditis (preponderantly involving the right bundle branch) syphilitic infection in the heart (gummatous or diffuse) acute diphtheria (when it is especially serious and likely to be fatal) rarely other infections such as from viruses or bacterial endocarditis and very rarely tumors and trauma

Of a series of 52 cases of intraventricular block 44 or 84.6 per cent were thought to be due to coronary disease 3 cases (5.8 per cent) were apparently rheumatic 3 cases were syphilitic and 2 cases were of unknown cause (White and Jones 1928)

Functional intraventricular block transient in occurrence is relatively infrequent It has however been noted as a toxic result of too much digitalis or quinidine or of other poisoning It may occur as the result of fatigue in very rapid heart action, as temporarily in atrial flutter without atrioventricular block

**Sex** Males show bundle branch block much more commonly than do females probably because of a higher incidence of serious coronary disease The ratio is about 3 to 1

**Age** Bundle branch block is much more common in older persons 80 per cent of the cases being more than 50 years old It is very rare in infancy and early childhood

**Pathology** In a few cases of established intraventricular block no pathologic change is found in the bundle branches but it is probable that in most of these exceptions there is a limited blood supply because of coronary disease In instances in which some temporary poison fatigue from tachycardia or unusual vagus stimulation is responsible naturally no pathologic change is to be expected functional and organic factors may however be combined It is usual to find some changes especially fibrosis in the bundle branches in pronounced degrees of intraventricular block but the search in the human heart is a difficult one and much experience and patience are required for identification of the bundle branches and their careful study as yet there is insufficient information about their structural pathology A source of confusion is that both bundle branches may show considerable pathologic change when the electrocardiogram indicates either left or right branch block or there may even be more change on the opposite side (Yater 1938) the explanation is probably that the structural changes alone are inadequate to account for the whole picture and that a few conducting fibers on one side may be more effective than a large number on the other side for some reason perhaps because of a difference in blood supply It is apparently rare for bundle branch damage or depression to be wholly unilateral

**Symptoms** There are no symptoms of bundle branch block There are frequently associated however the symptoms of angina pectoris and congestive failure and palpitation due to various complicating arrhythmias

**Signs** There are no characteristic signs of bundle branch block except the pathognomonic electrocardiograms on which the diagnosis depends (Figures 165 page 947, and 166 page 948) There may be in some cases reduplication of one or of both heart sounds due to the somewhat asynchronous contractions of the ventricles resulting from bundle branch block but this sign is not constant When both heart sounds are clearly reduplicated intraventricular block should be looked for

Usually heart disease is evident when there is bundle branch block Cardiac enlargement is a common finding but valvular disease is relatively infrequent Hypertension occasionally exists and there may be signs of heart failure Roentgen ray examination is of no particular help

**Course and prognosis** Bundle branch block of slight degree may be a relatively unimportant accidental discovery or it may be associated with serious and rapidly fatal heart disease such as extensive infarction from coronary thrombosis In some cases it exists unchanged for many years allowing full activity but in others it may change in the course of weeks or months increasing in degree along with symptoms and signs of progressive heart failure It may be entirely unimportant in rare cases occurring as a more or less transient effect of vagal stimulation or of fatigue in excessive tachycardia Of itself it is not fatal but each case must be analyzed carefully Although the prognosis is to be based largely on other evidence of heart disease the finding of true bundle branch block of high degree renders the prognosis necessarily more guarded The average survival time for 281 cases of right bundle branch block was 3.9 years and for 555 cases of left bundle branch block 3.3 years (see below) The 185 cases of right bundle branch block who survived the first year of follow up had an average survival time of 5.7 years and the 356 cases of left bundle branch block who survived the first year had an average survival time of 4.9 years From these figures it would appear that the right bundle branch block may show a slightly better prognosis than left bundle branch block however an analysis of the survival time at different age groups indicates that after the age of 50 there is only slight difference between the average survival periods of right and left bundle branch block either in the total number of patients or in the group who survived the first year

There seem to be two general clinical groups of cases with bundle branch block (1) that with a rapidly bad prognosis based largely on the presence of evidence of extensive heart disease usually considerable enlargement and some degree of myocardial or coronary insufficiency and (2) that with a good prognosis of years of life and activity in which the bundle branch block is the only abnormal finding despite this general trend accurate prognosis in an individual case is often difficult It is the general finding at present that the cases with the lesser grades of right bundle branch block (wide S waves in Lead I) survive the longest statistics are accumulating but are not yet fully adequate

Among others three series of cases of bundle branch block have been considered prognostically in recent years One series of 126 patients showed a high



mortality during the first year (60 cases nearly 50 per cent), 15 of the cases died during the next few years and 11 were still living 4 to 8 years after the discovery of the lesion neither the configuration of the electrocardiogram nor the duration of the QRS deflection seemed to be of prognostic significance (Kaplan and Katz 1939) On the other hand a series of cases reported by Perera Levine and Erlanger (1942) showed a considerably longer average survival time for right bundle branch block (3 years for 29 fatal cases) than for left (1 year and 2 months for 60 fatal cases) long time survivors in each group were still alive the longest exceeding 17 years for the right and 15 years for the left A third more recent series (Shreenivas et al 1950) referred to above has dealt with larger numbers over a longer interval A series of 281 cases of right bundle branch block electrocardiographed at the Massachusetts General Hospital gave the following statistical findings death within one year in 45 patients (16 per cent of the total series and 24 per cent of those traced) and survival of 72 cases for more than five years after the bundle branch block was discovered (27 per cent of the total series and 40 per cent of those who could be traced) In a consecutive series of 555 patients with left bundle branch block, also electrocardiographed at the Massachusetts General Hospital a survival period of less than one year was found in 170 (31 per cent of the total series and 32 per cent of those traced) and of more than five years after the bundle branch block was discovered in 121 (21 per cent of the series and 28 per cent of those who could be traced)

**Complications** There are no complications directly due to the bundle branch block unless in very rare cases both bundle branches are completely blocked with a resulting condition which is indistinguishable from atrioventricular block of this possible mechanism we have no definite clinical knowledge Conditions frequently complicating intraventricular block are atrioventricular block of all grades atrial fibrillation angina pectoris, myocardial infarction congestive heart failure pulsus alternans and hypertension

**Treatment** There is no direct treatment of the bundle branch block but therapy of any cause that may be recognized may not only help the underlying disease or disorder but also very rarely decrease or abolish the intraventricular block this may happen in the case of atrial flutter or paroxysmal tachycardia with functional bundle branch block and in syphilitic rheumatic or diphtheritic affection of the heart Complications such as congestive heart failure and angina pectoris should be treated without any regard to the presence of the bundle branch block

**Differential diagnosis** Bundle branch block must be differentiated from a normal ventricular mechanism and this can be done only by electrocardiogram electrocardiography also distinguishes the various types of intraventricular block as described above Even by electrocardiogram however it may be occasionally difficult in the presence of very rapid heart action to distinguish bundle branch block from ventricular paroxysmal tachycardia it may be necessary to wait till the pulse slows before differentiation is clear There is no particular condition pathologic or otherwise to be differentiated from

intraventricular block, except the anomalous state of the conducting system in which the impulse is transmitted with excessive speed to one ventricle or the other rather than delayed in the contralateral branch in such cases the *P R* interval is excessively short and that is the clue that makes the differentiation at once clear (Wolff Parkinson and White 1930)

#### WIDE *QRS* WAVE WITH SHORT *P R* INTERVAL

An odd electrocardiographic anomaly (Figure 168) probably congenital in origin has been found in healthy young persons prone to paroxysmal tachycardia (Wolff Parkinson and White 1930) it has the appearance of bundle branch block with short *P R* interval (0.1 second or less). The wide *QRS* waves may on occasion spontaneously or after exercise or atropine sud

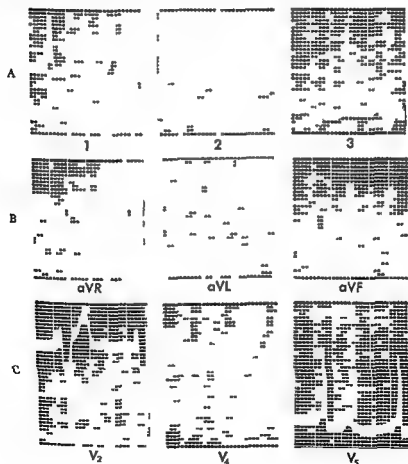


FIG 168 Electrocardiogram showing short *P R* and wide *QRS* waves (Wolff Parkinson White syndrome) Male age 43 (A) Bipolar limb leads 1, 2 and 3 (B) unipolar limb leads *aVR*, *aVL* and *aVF* (C) three precordial leads *V*<sub>2</sub>, *V*<sub>4</sub> and *V*<sub>5</sub> Time = 0.04 and 0.20 second amplitude 1 mm = 100 mv

denly give way to normal *QRS* waves with normal *P R* intervals. The total duration of the short *P-R* interval plus the wide *QRS* wave is well within normal limits and equal in the same subject to the duration of the normal *P R* interval plus the normal *QRS* wave to which the case may at times revert. A most certainly the correct explanation of this anomaly is that there is no bundle branch block at all and that the impulse travels much more rapidly than usual from atrium to one or the other ventricle either (1) by special conducting fibers from sinoatrial node or elsewhere in the atrium to one ventricle or the other (e.g. via a bundle of Kent Kent, 1893), or (2) by super-normal spread down one or the other bundle branch (thus representing a right or left *bundle branch acceleration* instead of the usual reversed left or right bundle branch block) or (3) less likely as the result of two interfering pacemakers one in the atria and the other in the ventricles (Hunter et al 1940) thus shortening the *P R* interval and giving rise to a *QRS* wave that in shape resembles that of bundle branch block, sometimes the impulse in any given case may pass through the short circuit and sometimes through the usual circuit in the bundle of His.

Almost all the patients have remained in good health but a few have succumbed in middle or in old age to such complications as coronary thrombosis or even apparently to a disturbed heart rhythm (as in a recent case of our own a woman aged 48 who died suddenly during or after a paroxysm of atrial fibrillation with an excessive heart rate of 300 or slightly more). Autopsies in 2 or 3 cases have apparently revealed an extra bundle (of Kent) (e.g. Ohnell 1940). The syndrome is not very rare it makes up about 5 per cent of cases with wide *QRS* waves and about 5 per cent of patients subject to paroxysmal tachycardia (Hunter et al 1940).

### SUDDEN DEATH

The most dramatic disorder of cardiovascular function is that which causes sudden death in fact it was such a source of concern to Pope Clement VI in Rome in the winter of 1705 to 1706 that he directed his physician Lancisi to study the problem by autopsies and otherwise and in 1707 one of the very few books on the subject was published by Lancisi. Sudden death is apparently due to an abrupt ventricular asystole (from standstill or fibrillation) quite possibly with an additional element of sudden depression of the central nervous system. No adequate reason may be found pathologically for such a death although there is usually evidence of considerable coronary or aortic disease consisting generally of marked sclerosis and narrowing of the coronary arteries or of syphilitic aortitis. Sudden death is quite a different matter from the more gradual death from asphyxia in heart failure or from massive pulmonary embolism or from cerebral hemorrhage.

Very few cases indeed are explained by cardiac or aortic rupture with abrupt exsanguination. It is most likely that the effective mechanism of the heartbeat itself is suddenly stopped by a great reflex vagal effect with paralysis

of the pacemakers or by the onset of ventricular fibrillation. Already a small group of electrocardiograms taken at the time of death under various conditions has been accumulated but we need many more. With the solution of the mystery there may come progress leading to the resuscitation of some of these victims. Epinephrine and other drugs injected directly into the heart and certain mechanical and electric stimulation such as massage during abdominal operations applied directly after rapid thoracotomy or from under the diaphragm, the prick of a needle with or without electric charge or even striking the chest wall have restored the circulation in some individuals whose hearts had stopped beating. Cardiac massage along with the maintenance of artificial respiration has proved the most consistent of the successful procedures to date (Dripps et al. 1948). Further discussion of cardiac standstill and ventricular fibrillation and possible resuscitation therefrom can be found in Chapter 33, pages 919 to 921 and in this chapter, pages 929, 930, 941 and 944.

An important note should be added herewith to this discussion, namely that rations of quinidine sulfate 3 gr four to six times a day may very possibly prevent the onset of ventricular tachycardia and fibrillation that leads to rapid death in some cases of fresh myocardial infarction or of a high degree of coronary insufficiency as indicated by angina pectoris decubitus (Borg 1939).

There has been in recent years a revival of interest in the pathologic findings on postmortem examination of persons who had died suddenly. I shall summarize four such analyses. Martland (1940) has told of his own experience with the autopsies of 2 000 individuals over the age of ten whose deaths were sudden but not the result of violence; the majority were between 40 and 65 and by far the larger number were males (1 680 or 84 per cent). Organic heart or aortic disease was present in 1 590 (79.5 per cent). 8 per cent had disease of the respiratory organs, 4 per cent of the head, and the remaining 8.5 per cent were subjects with miscellaneous conditions. Of the 1 590 cases of disease of heart or aorta, 1 115 (55 per cent of the total 2 000) were of the coronary or hypertensive type, 262 had syphilitic aortitis, 116 rheumatic heart disease, and 97 other types of heart disease. Among the coronary cases which numbered 731 (36.5 per cent of the total) there was coronary occlusion with acute thrombosis in 304 and without acute thrombosis in 314; the remaining 113 cases showing considerable atheroma without actual occlusion of the larger vessels. Well marked aneurysm of the left ventricle was present in 59 cases and rupture of the ventricular wall in 42 persons. Large hearts without much coronary disease and probably the result of hypertension occurred in 384 cases. Among the 262 syphilitics aneurysm of the aorta was found in 102 cases, aortic regurgitation in 70 and stenosis of the coronary ostia in 80. Rupture of the aorta had occurred in 37 persons of the total series. Aortic stenosis was found in 32 cases and pulmonary embolism in 10. There was one young colored man who showed at autopsy no abnormalities whatsoever, marked apprehension about an impending minor surgical procedure immediately preceded his sudden death, and it was thought that this was an almost

unique example of an overwhelming nervous (vagal) depression of the heart beat with resulting death from fright'

Analysis of another group of 123 autopsies in cases of unexplained sudden death (Jeckeln 1940) showed two thirds to have been the result of heart disease with coronary lesions forming the great majority, six times more often in men than in women. Excessive filling of the stomach with food was frequently found in these fatal coronary cases. In 7 cases death was due apparently to syphilitic aortitis and 5 cases had aortic stenosis while only 1 had mitral stenosis (with coronary sclerosis). In 2 cases death resulted from rupture of the aorta and in 3 others from apoplectic cerebral hemorrhage. Ruptured aneurysm at the base of the brain (giving rise to a subarachnoid hemorrhage) was found in as many as 19 cases. There were 30 cases of sudden death in children, 6 of which were stillborn, the others being due to a variety of infections, traumatic brain lesions sustained at birth and acute respiratory disorders.

Lisa (1939) noted the findings in 41 persons dying sudden cardiac deaths: acute coronary thrombosis was present in 10, acute coronary insufficiency was apparently responsible in 5, more acute endocarditis was found in 5, rheumatic heart disease in 4, syphilis in 8, and pulmonary lesions in 2. 5 cases were infants or children and the remaining 2 were entirely unexplained.

More recently Helpern and Rabson (1945 and 1947) have reported their experience. These authors have analyzed in considerable and interesting detail 2,030 consecutive cases of sudden and unexpected death in the Borough of Manhattan from January 1937 to July, 1943. Table 14 below gives the details of this analysis: 912 cases or 44.9 per cent involved the heart and aorta, 468 cases or 23.1 per cent involved the respiratory tract, 367 or 17.9 per cent involved the brain and meninges, 198 or 9.7 per cent involved the digestive and genitourinary tracts. There were 90 miscellaneous cases or 4.4 per cent. If we include cases of pulmonary embolism and of cerebral vascular accidents with the cases of heart and aorta to complete the cardiovascular responsibility we have a total of 1,195 cases or 59.0 per cent. The greatest incidence of all these cases was in the decade from 45 to 54 years of age inclusive. Males were preponderant over the females in a ratio of 4 to 1. Among the coronary cases 80 per cent died instantly. Also among the coronary cases three fourths showed no grossly fresh thrombosis.

In closing this chapter and the book itself may I suggest that after all neither a high even 100 per cent mortality from cardiovascular disease nor sudden death itself are to be regretted provided they take place at an advanced age after a healthy and happy and useful life right up to the last minute. In fact this is actually an ideal goal toward which man may strive for it means the eradication not only of other diseases such as the infections of the past and the cancers, accidents and the wars of the present but also the control of the serious cardiovascular threats (such as hypertension and coronary atherosclerosis) to the lives of our youth and middle aged which bid fair to trouble

us for still some years to come. Furthermore we physicians must work hand in hand in our labors with our pioneering colleagues in the gravely needed advances in the social, economic and spiritual fields of human endeavor. Those of us who have striven during the last generation to probe a little into the depths of our ignorance can turn over with confidence to our successors the far more important task of bringing to pass the aim expressed in the first sentence of this closing paragraph.

Table II

ANALYSIS OF 2 030 AUTOPSIED CASES OF  
SUDDEN AND UNEXPECTED NATURAL DEATH<sup>1</sup>

Cause	Identified Diseases	Number	Percentage of Group	Percentage of Total (2 030)
Heart and Aorta 917 Cases (44.9%)	Coronary artery disease	617	67.7	30.4
	Syphilitic aortitis	107	11.7	5.3
	Valvular disease	83	9.2	4.1
	Cardiac hypertrophy	35	3.8	1.7
	Spontaneous rupture of aorta	25	2.7	1.2
	Others	45	4.9	2.2
Respiratory 468 Cases (23.1%)	Lobar pneumonia	176	37.6	8.7
	Bronchitis bronchopneumonia	133	28.4	6.5
	Pulmonary tuberculosis	111	23.9	5.4
	Pulmonary embolism and infarction	31	6.7	1.6
	Others	60	12.8	2.9
Brain and Meninges 367 Cases (17.9%)	Cerebral hemorrhage	110	30.4	5.4
	Subarachnoid hemorrhage	93	25.7	4.6
	Cerebellar hemorrhage	11	3.0	0.6
	Pontine hemorrhage	11	3.0	0.6
	Cerebral thrombosis and embolism	7	2.5	1.3
	Meningitis	38	10.6	1.9
	Brain tumor	29	8.0	1.4
	Others	43	11.8	2.1
Digestive and Urogenital		198		9.7
Miscellaneous		90		4.4

<sup>1</sup>Helpert, M. Sudden and Unexpected Natural Death. Read at the Fifty-sixth Annual Meeting of the Association of Life Insurance Medical Directors of America, October 23-4, 1947.

## BIBLIOGRAPHY

HEART BLOCK (SINOATRIAL ATRIOVENTRICULAR AND INTRAVENTRICULAR)  
 ATRIOVENTRICULAR NODAL RHYTHM MORGAGNI ADAMS STOKES  
 SYNDROME SUDDEN DEATH

Sinoatrial Bradycardia and Arrhythmia Sinoatrial Block and Intra atrial Block. Atrial Standstill Carotid Sinus Reflex

- Adams H B and Hand L V Twenty Minute Cardiac Arrest with Complete Recovery *JAMA* 1942 CXVIII 133
- Czermack J Ueber mechanische Reizung des Nervus vagus beim Menschen *Jena Ztschr f Med u Naturwiss* 1866 II 384
- DeCastro F Sur la structure et l'innervation du sinus carotidien de l'homme et des mammiferes Nouveaux faits sur l'innervation du glomus caroticum *Trav Lab Recherch* Madrid 1928 XXV 331
- Faulkner J M Significance of Sinus Arrhythmia in Old People *Am J Med Sc* 1930 CLXXX 42
- Ferris E B Jr Capps R B and Weiss S "Carotid Sinus Syncope and Its Bearing on Mechanism of the Unconscious State and Convulsions Study of 32 Additional Cases *Medicine* 1935 XIV 377
- Ganter G and Zahn A Über die Beziehungen der Nervi vagi zu Sinusknoten und atrioventrikularknoten *Pflügers Arch f d ges Physiol* 1913 CLIV 492
- Hering H E Der Karotisdruckversuch *Munch med Wchnschr* 1903 LXX 1287
- Heymans C Le sinus carotidien et les autres zones vasosensibles réflexogènes *Preses Universitaires de France* Paris 1929
- Laslett E E Syncopal Attacks Associated with Prolonged Arrest of the Whole Heart. *Quart J Med* 1908-9 II 347
- Levine S A Observations on Sino Auricular Heart Block *Arch Int Med* 1916 XVII 153
- Waller A "Experimental Researches on the Functions of the Vagus and the Cervical Sympathetic Nerves in Man *Proc Roy Soc London* 1861 XI 302
- Weiss S and Baker J P The Carotid Sinus Reflex in Health and Disease Its Role in the Causation of Fainting and Convulsions *Medicine* 1933 XII 297
- White P D Auricular Standstill *Boston M & S J* 1916 CLXXV 243
- Extreme Bradycardia (Below the Rate of 40) in Athletes Especially Distance Runners *Letter JAMA* 1942 CXX 642

Recent References (1944-1950)

- Askey J M Hemiplegia Following Carotid Sinus Stimulation " *Am Heart J* 1946 XXXI 131
- Cattell R H and Welch M L Carotid Sinus Syndrome Surgical Treatment " *Surgery* 1947 XXII 59
- Iandolo C and Puddu V La Sincope *Fisiopatologia e Clinica dell'anossia Cerebrale* *Acta L Pozzi* Rome 1949
- Jervell O Bradycardia *Nord Med* 1946 XXII 2575
- Leger L and Coste M Syncopes a repetition hees a une hyperréflexivité sinuotale Guérison par énervation sinocarotidienne *Presse méd* 1947 LV 174
- Magnusson P Auricular Standstill *Acta med Scandinav* 1946 CXXIII 519

Atrioventricular Nodal Rhythm and Ventricular Escape

- Cutts F H The Transitions Between Normal Sinus Rhythm Ventricular Escape A V Nodal Rhythm and A V Dissociation *Am Heart J* 1937 XIII 451
- Gallavardin L Dufourt P and Petzetakis Automatismes ventriculaires Intermitte spontane ou provoque par la compression oculaire et l'injection d'atropine dans les bradycardias totales " *Arch d mal d coeur* 1914 VII 1

White P D "A Study of Atrioventricular Rhythm Following Auricular Flutter" *Arch Int Med* 1915 XVI 517

Ventricular Escape with Observations on Cases Showing a Ventricular Rate Greater Than That of the Auricles *Arch Int Med* 1916 XVIII 244

Wilson F N "The Production of Atrioventricular Rhythm in Man after the Administration of Atropin" *Arch Int Med* 1915 XVI 989

#### Recent References (1944-1950)

Langendorf R, Simon A J and Katz L N "A V Block in A V Nodal Rhythm" *Am Heart J* 1944 XXVII 209

#### Atrioventricular Block Morgagni Adams Stokes Syndrome

Adams R Cases of Diseases of the Heart Accompanied with Pathological Observations *Dublin Hosp Rep* 1827 IV 353

Bourne G "Notes on a Case of Heart Block Whose Grade Was Decreased by Inspiratory Increase in Sympathetic Tone" *St Bartholomew's Hosp Rep* 1928 LXI 146

Faulkner J M "An Extraordinary Degree of Partial Heart Block. Report of a Case in Which the P R Interval Exceeded the R R Interval" *Am Heart J* 1935 X, 969

Galabin A L "On the Interpretation of Cardiographic Tracings and the Evidence Which They Afford as to the Causation of the Murmurs Attendant upon Mitral Stenosis" *Guy's Hosp Rep* 1875 3rd Series XX 261

Graybiel A and White P D Complete Auriculoventricular Dissociation. Clinical Study of Seventy-two Cases with Note on Curious Form of Auricular Arrhythmia Frequently Observed" *Am J M Sc* 1936 CXCI 334

Hoff H E and Nahum L H "The Role of Adrenaline in the Production of Ventricular Rhythms and Their Suppression by Acetyl B Methylcholine Chloride" *J Pharmacol & Exper Therap* 1934 LII 235

Langendorf R and Katz L N Unusual Arrhythmias Due to Multiple Sites of Conduction Delay in the A V Junction in Cases with a Subsidiary Ventricular Pacemaker Located Above the Bifurcation of the Common Bundle. *Am Heart J* 1942 XXIV 31

Lewis T and Mack E G Complete Heart Block and Auricular Fibrillation. *Quart J Med* 1910 III 273

Lewis T, White P D and Meakins J "The Susceptible Region in A V Conduction" *Heart* 1914 V 289

Mitchell F V, Fetter D B Jr and Hollander A G Complete Heart Block Complicating Pregnancy" *Am J Obst & Gynec* 1943 XLV 340

Morgagni J B *De Sedibus et Causis Morborum per Anatomen indagatis Libri Quinque* Ex Typographia Remondiniana, Venice 1761

Odrizola E Adams Stokes Disease with One Heart Beat Per Minute *An d la Facultad d med d Lima* 1920 III No 16 p 5

Perry C II and Rogers II "Lymphangio-Endothelioma of Heart Causing Complete Heart Block" *J Path & Bact* 1934 XXXIX 281

Salcedo Salgar J and White P D "The Relationship of Heart Block, Auriculoventricular and Intraventricular to Clinical Manifestations of Coronary Disease, Angina Pectoris and Coronary Thrombosis" *Am Heart J* 1935 X 1067

Schmidt Weyland P "Totaler Herzblock nach Schussverletzung vor 36 Jahren" *Deutsch med Wchschr* 1931 LVII 2014

Smith H L Complete Heart Block of Thirty Years Duration *Am Heart J* 1933 VIII 719

Stokes W Observations on Some Cases of Permanently Slow Pulse *Dublin Quart J M Sc* 1846 II 73

White P D Un cas de dissociation auriculo ventriculaire complete avec reductions transitoires a moitie de la frequence ventriculaire *Arch d mal d coeur* 1918 XI 352

White P D and Jones T D Heart Disease and Disorders in New England" *Am Heart J* 1928 III 307

White P D and Sprague H B "Electrocardiography of 10 000 Patients at the Massachusetts General Hospital from 1914 to 1931" *Kasan Med Jour USSR*, 1931 XXVII 381



Yater W M and Cornell V H "Heart Block Due to Calcareous Lesions of the Bundle of His: Review and Report of a Case with Detailed Histopathologic Study" *Ann Int Med* 1935 VIII 777

*Recent References (1944-1950)*

- Beard O W and Decherd G M Jr "Variations in the First Heart Sound in Complete A V Block" *Am Heart J* 1947 XXXIV 809
- Campbell, W "Complete Heart Block" *Brit Heart J* 1944 VI 69
- Goldfinger D, Schreiber W and Wosika P H "Permanent Heart Block Following German Measles" *Am J Med* 1947 II 320
- Mahaim I "Kent's Fibers and the A V Paraspecific Conduction Through the Upper Connections of the Bundle of His-Tawara" *Am Heart J* 1947 XXXIII 651
- Maldonado Aliende I "Bloqueo cardiaco congenito embarazo y bloqueo" *Rev argent de cardiol* 1950 XVII 137
- Menon T B and Prasada Rao C K "Tuberculosis of the Myocardium Causing Complete Heart Block" *Am J Path* 1945 XXI 1193
- Moe T, Morgagni, Adams "Stokes Attacks Caused by Transient Recurrent Ventricular Fibrillation in a Patient Without Apparent Organic Heart Disease" *Am Heart J* 1949 XXXVII 811
- Stern V S "Stokes Adams Attacks in a Child" *Brit Heart J* 1944 VI 66
- Towers J R H and Bremer C "Complete Heart Block in Young People" *Brit Heart J* 1947 II 906

**Intraventricular (Bundle Branch) Block**

- Barker P, MacLeod A G and Alexander J "The Excitatory Process Observed in the Exposed Human Heart" *Am Heart J* 1930 V 720
- Bohning A, Katz L N and Langendorf R "The Distribution of Surface Potentials on the Chest in Intraventricular Block" *Am Heart J* 1941 XXII 778
- Carter E P "Clinical Observations on Defective Conduction in the Branches of the Auriculo-ventricular Bundle: A Report of Twenty-two Cases in Which Aberrant Beats Were Obtained" *Arch Int Med* 1914 XIII 803
- Comeau W J, Hamilton J G M and White P D "Paroxysmal Bundle Branch Block Associated with Heart Disease" *Am Heart J* 1938 XV 276
- Eppinger H and Rothberger J "Ueber die Folgen der Durchschneidung der Tawarschen Schenkel des Reizleitungssystems" *Ztschr f klin Med* 1910 LXX 1
- Kaplan L G and Katz L N "The Prognosis of Intraventricular Block" *Am Heart J* 1939 XVIII 145
- MacLeod A G, Wilson F N and Barker P S "The Order of Excitation of the Ventricles in Bundle Branch Block" *J Clin Investigation* 1930 IX 15
- Mahaim I, Winston M R and Roesler H "Bilateral Missed Block" *Am Heart J* 1943 XXV 251
- Mann H "Interpretation of Bundle Branch Block by Means of the Monocardiogram" *Am Heart J* 1931 VI 447
- Oppenheimer H S and Oppenheimer E T "The Site of the Lesions in Ten Cases of Intraventricular Block Including Bundle Branch Block and Arborization Block" *Tr A Am Physicians* 1930 XLV 427
- Perera G A, Levine S A and Erlanger H "Prognosis of Right Bundle Branch Block: Study of 104 Cases" *Brit Heart J* 1942 IV 35
- Purkinje J E "Mikroskopisch neurologische Beobachtungen" *Arch f Anat Physiol u wiss Med* 1845 p 281
- White P D and Jones T D "Heart Disease and Disorders in New England" *Am Heart J* 1928 III 302
- White P D and Sprague H B "Electrocardiography of 10,000 Patients at the Massachusetts General Hospital from 1914 to 1931" *Kasan Med Jour USSR*, 1931 XXVII 381
- Wilson F N "Concerning the Form of the QRS Deflections of the Electrocardiogram in Bundle Branch Block" *J Mt Sinai Hosp* 1942 VIII 1110
- Wilson F N, Johnston F D, Hill I G W, MacLeod A G and Barker P S "The Significance of Electrocardiograms Characterized by an Abnormally Long QRS Interval and by Broad S Deflections in Lead I" *Am Heart J* 1935 IX 459

- Wilson F N MacLeod A G and Barker F S "The Order of Ventricular Excitation in Human Bundle Branch Block" *Am Heart J* 1932 VII 105
- Wood F C Jeffers W A and Wolferth C C Follow Up Study of Sixty Four Patients with a Right Bundle Branch Conduction Defect" *Am Heart J* 1935 X 1056
- Yater W M "Pathogenesis of Bundle Branch Block Review of the Literature Report of Sixteen Cases with Necropsy and of Six Cases with Detailed Histologic Study of the Conduction System" *Arch Int Med* 1938 LXII 1

## Recent References (1944-1950)

- Bates W H Bundle Branch Block with Spontaneous Remission After 18 Months *Arizona Med* 1949 VI 21
- Cervia Cabrera T Bloqueo de rama con mas de diecisiete anos de supervivencia" *Clinica y Laboratorio Zaragoza* 1949 XLVII 432
- Chakravarti H "Bilateral Bundle Branch Block" *Indian Heart J* 1950 II 57
- Kalet J "Bundle Branch Block, with Spontaneous Remission After Four Years" *Am Heart J* 1945 XXIX 170
- Messer A L Johnson R P Shreenivas and White P D Prognosis in Bundle Branch Block. I Factors Influencing the Survival Period in Right Bundle Branch Block II Factors Influencing the Survival Period in Left Bundle Branch Block III A Comparison of Right and Left Bundle Branch Block With a Note on the Relative Incidence of Each" *Am Heart J* 1950 XL 891 and 1951 XLI 239
- Myers G B QRS T Patterns in Multiple Precordial Leads That May Be Mistaken for Myocardial Infarction III Bundle Branch Block" *Circulation* 1950 II 60
- Pantridge J F Abildskov J A Burch G F and Cronvich J A "A Study of the Spatial Vectorcardiogram in Left Bundle Branch Block" *Circulation* 1950 I 893
- Pfeiffer P H and LaDue J S Major Surgical Operations in the Presence of Bundle Branch Block A Study of the Operative Risk in 59 Patients *Am J M Sc* 1949 CCXVII 369
- Rasmussen H and Moe T Pathogenesis of Left Bundle Branch Block" *Brit Heart J* 1948 X 141
- Sodi Pallares D Thomsen P and Soberon J "New Contributions to the Study of the Intracavity Potential in Cases of Right Bundle Branch Block in the Human Heart" *Am Heart J* 1948 XXXVI 1

## Short P R Interval and Wide QRS Wave

- Butterworth J S and Poindexter C A Short P R Interval Associated with a Prolonged QRS Complex A Clinical and Experimental Study *Arch Int Med* 1942 LXIX 437
- Holzmann M and Scherf D Über Elektrokardiogramme mit verkürzter Vorhof-Kammer Distanz und positiven P Zacken *Ztschr f klin Med* 1932 CXXI 404
- Hunter A Papp C and Parkinson J The Syndrome of Short P R Interval Apparent Bundle Branch Block and Associated Paroxysmal Tachycardia *Brit Heart J* 1940 II 107
- Kent A F S Researches on the Structure and Function of the Mammalian Heart *J Physiol* 1893 XIV 233
- Levine S A and Beeson P B "The Wolff Parkinson White Syndrome with Paroxysms of Ventricular Tachycardia" *Am Heart J* 1941 XXII 401
- Ohnell R F "Postmortem Examination and Clinical Report of a Case of the Short P R Interval and Wide QRS Wave Syndrome" *Cardiologia* 1940 IV 249
- Wolff L Parkinson J and White P D Bundle Branch Block with Short P R Interval in Healthy Young People Prone to Paroxysmal Tachycardia *Am Heart J* 1930 V 685
- Wood F C Wolferth C C and Geckeler D Histologic Demonstration of Accessory Muscular Connections between Auricle and Ventricle in a Case of Short P R Interval and Prolonged QRS Complex *Am Heart J* 1943 XXV 454

## Recent References (1944-1950)

- Goldberg H H and Lewis S M "Acute Myocardial Infarction and the Wolff Parkinson White Syndrome" *Am Heart J* 1950 XL 614

- Grishman A Kroop I G and Steinberg M F "The Course of the Excitation Wave in Patients with Electrocardiograms Showing Short P R Intervals and Wide QRS Complexes (Wolff Parkinson White Syndrome)." *Am Heart J* 1950 XL, 554
- Littmann D "Observations on the Fate of the Accessory Conductor in Wolff Parkinson White Syndrome Report of a Case Demonstrating Return to Normal Conduction Following Acute Illness" *Ann Int Med* 1949 XXX 423
- Malinow M R and Langendorf R "Twenty Year Follow up in a Case of Wolff Parkinson White Syndrome" *Ann Int Med* 1950 XXXIII 227
- Rinzler H "Coexistence of the Wolff Parkinson White Syndrome and Organic Heart Disease" *New York State J Med* 1948 XLVIII 1617
- Segers M Sanabria T Lequime J and Denolin H "Le syndrome de Wolff Parkinson White Mise en evidence d'une connexion A V septale directe" *Acta Cardiologica* 1947 II 21
- Soderstrom N "Absence of Accessory A V Muscle Connections in a Case with Pre excitation Electrocardiogram Report of Clinical and Post Mortem Findings." *Acta med Scandinav* 1948 170 Suppl 119
- Vega Diaz, F "Sindromes Clinicoelectrocardiograficos de WPW Contribucion al conocimiento de su fisiopatologia" *Revista Clinica Espanola* 1944 VIII 287
- Willius F A and Carryer H M "Cardiac Clinics CXVII Electrocardiograms Displaying Short P R Intervals with Prolonged QRS Complexes An Analysis of Sixty five Cases" *Proc Staff Meet Mayo Clin* 1946 XXI 438
- Wolff L and White P H "Syndrome of Short P R Interval with Abnormal QRS Complexes and Paroxysmal Tachycardia" *Arch Int Med* 1948 LXXXII 446

### Sudden Death

- Borg J E "Observations on the Occurrence and Prevention of Sudden Death" *Tr Am Therap Soc* 1939 XXXIX 115
- Goldbloom A and Wigglesworth F W "Sudden Death in Infancy" *Canad M A J* 1938 XXXVIII 119
- Hamilton R L and Robertson H "Electrocardiographic Studies of the Dying Heart in Angina Pectoris" *Canad M A J* 1933 XXIX 122
- Hamman L "Sudden Death" *Bull Johns Hopkins Hosp* 1934 LV 387
- Jeckeln E "Ueber plotzliche Todesfalle" *Deutsch med Wchnschr* 1940 LXVI 1 46
- Lancisi J M "De Subitaneis Mortibus" J F Buagni Rome 1707
- Lisa J R "Pathologic Findings in the Heart in Sudden Cardiac Deaths" *Ann. Int Med* 1939 XII 1969
- Martland H "Sudden Deaths with Reference to Their Prevention" *Proc New England Heart A* 1940 p 42
- Moritz A R "Sudden Death" *New England J Med* 1940 CCXXIII 798
- Munck W "Sudden Death from Heart Failure in Adults" *Ugeskr f Laeger Copenh* 1931 XCIII 787
- Reuter H "Ueber den plotzlichen Herztod und dessen Nachweis an der Leiche" *Bien klin Wchnschr* 1926 XXXIX 1086

### Recent References (1944-1950)

- Helpman M., and Rabson S M "Sudden and Unexpected Natural Death—General Considerations and Statistics" *New York State J Med* 1945 XLV 1197
- Jellinek S "Dying Apparent Death and Resuscitation" *Bailliere Tindall and Cox* 1947 and Williams and Wilkins Baltimore Md 1947
- Moritz A R and Zamcheck N "Sudden and Unexpected Deaths of Young Soldiers Diseases Responsible for Such Deaths During World War II" *Arch Path* 1946 XLII 459
- Munck W "Pathologic Anatomy of Sudden Heart Death" *Acta Path & Microbiol Scand* 1946 XXIII 107
- Rabson S M "Sudden and Unexpected Natural Death V Causes of Death Classified by Sex and Age" *Arch Int Med* 1950 LXXXVI 361
- Stroud M W and Feil H H "The Terminal Electrocardiogram Twenty Three Case Reports and a Review of the Literature" *Am Heart J* 1948 XXV 910

When the cause of the hyperglycemia is apparent it is suggested that it should not be called diabetes mellitus but instead be referred to as the hyperglycemia of that particular disease state. Thus one would speak of the hyperglycemia of Cushing's syndrome or of icteremia and confine the term diabetes mellitus to those conditions in which the hyperglycemia is of uncertain or unknown etiology.

**History**—The disease was well known to the ancients. Aretaeus in the first century used the word diabetes, named from the Greek word meaning a syphon. Due to the polyuria dominating the picture Galen thought that the kidneys allowed fluid to "run through" without alteration. In India the sweetness of the urine had been recognized for many centuries before Dobson, in 1775 obtained a sugar by evaporation. This sugar was later proved to be the same as that in grapes by Chevreul in 1815. Little further advance was made until von Mering and Minkowski in 1889 to 1892, produced the diabetic state in dogs by extirpation of the pancreas. For many years investigators the world over attempted to produce a nontoxic pancreatic extract that would have a specific effect upon the blood sugar of the diabetic dog. Little success was attained until in 1921 the work of Banting and Best, with the chemical assistance of Collip proved the possibility of preparing such a pancreatic extract containing the desired active principle. This hormone has been named *insulin*.

**Incidence**—Although diabetes is a common disease in many countries it is difficult for several reasons to arrive at an accurate estimate of its true incidence. It is usually considered that a fair reflection of the incidence of a possible fatal disease may be obtained from its death rate. But in the case of diabetes this record does not represent the total number of people with this disease who die. In the first place the primary cause of death in a diabetic may be recorded as tuberculosis, cancer, heart disease, etc., and second it may be considered as an incidental finding because the diabetic state is not recognized or because the doctor may be consulted in the terminal stage of some other illness and not have an opportunity to uncover the diabetes. The death rate from diabetes per 100,000 in the United States has increased from 9.7 in 1900 to 26.1 in 1944, but from 1940 to 1944 it has remained practically stationary (26.6 compared to 26.4). Joslin estimates that this represents at the most about two thirds of the people with this disease.

The total number of persons with diabetes in the United States (and proportionately in Canada) is variably estimated from 460,000 to 725,000. But Joslin, taking into consideration that in only two thirds of the death certificates of diabetes is the disease recorded, estimates that there were probably at least 1,000,000 diabetics in the United States in 1946.

It must not be taken that the incidence of the disease is uniform throughout the population. There are a number of conspicuous divergences of which the following are the more important and here the death rates will be taken as the index. The death rate per 100,000 varies with age. It increases in progressive decades as the following will show. In 1941 to 1945 the death rate under 25 was 1.5; between 25 and 44 it was 4.4; and from 45 to 74 it was 89. Furthermore, there has been an actual change in these relations over

recent years as in 1911-1915 the rates were 30.72 and 63.7 respectively. This improvement has been due to two factors, namely, since the introduction of insulin therapy there has been a conspicuous reduction in diabetic mortality in persons under 50 and particularly in children. Furthermore, the death rate and the incidence of diabetes rises within the individuals in the upper age groups. Therefore, as the life expectancy has increased since 1900 from 48 years in males and 51 in females to 63 and 68 respectively, in 1943 there are more people in the age groups where diabetes is most frequent. This relative increase in these people has been further accentuated by the prolongation of life due to insulin. It must not be inferred from this that diabetes is an old person's disease. The age at death might seem to indicate this, but Joslin has pointed out that the age of onset is under 50 in 57 per cent of males and 49 per cent of females and in approximately 73 per cent the onset is between 30 and 50 years of age.

**Sex**—At the turn of the century the reported incidence in males was definitely greater (roughly two to one) than in females. During the past fifty years this ratio has practically been reversed. Joslin attributes this to two principal reasons: (1) the greater attention being given to the health of women and (2) the increase in the number of women in the upper decades. This change not only holds for the United States but for most countries of the world.

**Race**—The high incidence of diabetes amongst the Jewish race is well known. It has also been shown that the age of onset is earlier than in the general population. What is not usually appreciated is its relatively high incidence amongst the Irish in the United States as compared to the rate in Ireland. Joslin attributes this to the fact that the general well-being and prosperity of the Irish in North America is much higher than in Ireland itself and further that during the time covered by his studies a disproportionate number of the Irish engaged in the liquor business. Rose has pointed out that in Bengal amongst the large well-educated classes in 2000 cases 68.2 per cent were Hindus, 14.6 per cent Mohammedans, 2.1 per cent other castes and 15.1 per cent Europeans. But he does not take into account the relative populations. However, he further records for Calcutta an overall increase of rate per 100,000 of 5.2 in 1929, 10.4 in 1933 and 20.7 in 1935. This startling increase would seem to be due to some factor other than an etiological one such as better diagnosis. Mills has on the other hand reported a low incidence of this disease in China and quoted others on its rarity and mildness in Japan and the Philippines. India in general, Sudan, West Africa and Venezuela. The clue to these variations is suggested to be an etiological one of prosperity and overindulgence in food and drink as intimated by Joslin for the Irish. It has also been found that the incidence of diabetes is higher in the urban as compared to the rural population. This would tempt one to make a generalization that the incidence of this disease is greatest in countries where the urban population predominates and the standard of living is high.

**Etiology**—As stated by the earlier investigators heredity still stands today as the basis upon which diabetes rests. There are other factors such as obesity and infections which play a contributing part.

betics was unable to demonstrate any microscopic changes in the pancreatic islets in 20 per cent of the patients. Although it was recognized that histological appearance may not be an adequate criterion of the functional status of an endocrine gland this observation directed attention to other possible causes of the metabolic disturbance associated with this disease. That other factors might be involved was also indicated from a comparison of the insulin requirements of patients rendered diabetic by complete pancreatectomy with those who have spontaneous diabetes mellitus. The former usually require no more than 30 units of insulin daily for adequate control of the blood glucose level while patients with spontaneous diabetes frequently require more.

Although in most patients with diabetes mellitus it cannot be proved that insulin deficiency is the primary cause, in some cases it can be inferred that destruction of the pancreas leading to insulin deficiency is responsible for the hyperglycemia. Of those diseases of the pancreas that may result in diabetes the most important are the following:

- 1 Acute and chronic pancreatitis
- 2 Carcinoma
- 3 Hemochromatosis
- 4 Syphilis (a very rare cause)

In those cases of diabetes mellitus in which the primary cause might be an extrapancreatic factor insulin deficiency may still play an important role in the continuation of the diabetic state. Evidence for this statement is provided by the recent experiments of Dohm and Lukens which demonstrated that the injection of glucose to normal cats for some weeks resulted in sufficient degeneration of the islet cells so that in spite of discontinuation of glucose administration the diabetic state persisted. These observations indicate that hyperglycemia per se can produce islet damage and insulin deficiency and support the view that in the treatment of diabetes mellitus one of the important objectives is the maintenance of the blood sugar within normal limits.

From this discussion it is apparent that in those cases of hyperglycemia of unknown etiology i.e. diabetes mellitus there is as yet no convincing proof that insulin deficiency is the primary cause of the carbohydrate disturbance. *However it must be emphasized that regardless what the cause may prove to be from the point of view of practical management these patients should be looked upon as being unable to provide a sufficient amount of endogenous insulin to meet their metabolic requirements.*

**ADRENAL.** The hormones of the cortex and the medulla affect the metabolism of carbohydrate. The administration of certain adrenal steroids (those with an oxygen atom on carbon 11 of the steroid nucleus such as Kendall's compound I) to rats results in a diabetic state characterized by marked insulin resistance. That overproduction of adrenocortical steroids can also produce hyperglycemia in man is indicated by the high incidence of hyperglycemia (approximately 90 per cent) in patients with Cushing's syndrome. Further evidence that the adrenal is primarily responsible for the diabetic state in such patients is the fact that when the disease is associated with an

adenoma of the adrenal cortex its successful removal is almost invariably followed by a disappearance of the hyperglycemia. In patients with diabetes mellitus who do not have Cushing's syndrome there is at present no convincing evidence that overactivity of the adrenal cortex is an etiological factor.

The frequent association of hyperglycemia with pheochromocytoma which disappears with resection of the tumor indicates that the overproduction of epinephrine is effective in elevating the blood glucose. But there is nothing to suggest that the medulla of the adrenal gland is responsible for the carbohydrate disturbance in diabetes mellitus.

**PITUITARY.** There is abundant evidence to indicate that certain of the hormones of the anterior pituitary gland play an important part in the regulation of carbohydrate metabolism. That overproduction of such hormones may be responsible for the development of a diabetic state is a possibility which is supported by the experimental production of hyperglycemia in animals by the administration of suitable pituitary extracts. Such extracts can produce experimental diabetes in at least two ways, one of which is mediated through the adrenal cortex. Thus the hyperglycemia which follows the administration of pituitary adrenocorticotrophic hormone is a consequence of increased production of adrenocortical hormones while that which follows the administration of the so called 'diabetogenic hormone' is not (Young).

The Coris have shown that the carbohydrate active anterior pituitary extracts depress the activity of the enzyme hexokinase in vitro. Since the action of this enzyme is essential for the normal utilization of glucose this is probably the mechanism by which the diabetogenic extracts of the pituitary produce hyperglycemia. It is of considerable importance that this inhibiting effect which is enhanced by the adrenocortical steroids is neutralized by insulin.

More direct evidence that the anterior pituitary gland may play some part in the etiology of human diabetes mellitus is provided by the recent observations that the administration of pituitary adrenocorticotrophic hormone to normal human subjects results in the temporary production of hyperglycemia and glycosuria. At present however the anterior pituitary can only be invoked in explaining the hyperglycemia which is associated with acromegaly. Both the incidence (approximately 30 per cent) of hyperglycemia in such patients and the amelioration which frequently follows resection of the acidophilic adenoma are strong evidence that the hyperglycemia in these patients is due primarily to increased secretion of pituitary hormones. In some cases the diabetic state may continue even when the tumor appears to have entered an inactive phase. In such cases the continuation of the diabetic state may be the result of a secondary insulin deficiency as described under the pancreas. These clinical findings have a counterpart in the experimental animal since Young has succeeded in producing hyperglycemia which persists after cessation of injection of pituitary extracts. This persistent hyperglycemia is associated with lesions of the islet cells which are probably secondary to the pituitary induced hyperglycemia.

**THYROID.** Although the thyroid hormone may play some part in regulating the blood sugar concentration it has not been possible to produce per-

ment hyperglycemia experimentally by the administration of this hormone. However, the incidence of hyperglycemia in patients with thyrotoxicosis is two to three times that in the general population. The correction of hyperthyroidism in such patients often results in an amelioration of the diabetic state and it seems likely that the overproduction of thyroid hormone is responsible for intensifying a latent or mild diabetes but is not the primary cause.

**Liver**—The liver normally plays an important part in the metabolism of carbohydrate. It stores the ingested carbohydrate as glycogen which it later converts to glucose in order to maintain the blood glucose concentration in the fasting state. It also is the chief site where noncarbohydrate substances are converted to glucose (gluconeogenesis). Since the storage of glucose as glycogen in the liver is one of the important ways by which the organism avoids an excessive elevation of the blood glucose following a meal it has been suggested that a failure of this to occur might result in hyperglycemia. It is undoubtedly true that some patients with hepatic dysfunction which may be associated with sick euthyrosis may have an impaired carbohydrate tolerance which manifests itself usually as a postprandial hyperglycemia. As yet there is no evidence to indicate that hepatic insufficiency plays an important role in the etiology of the diabetic state except in those patients with overt hepatic disease. Since the liver occupies a central position in the homeostatic mechanisms which regulate the concentration of blood glucose, it will not be at all surprising if future work reveals that hepatic dysfunction is important in the etiology of diabetes mellitus.

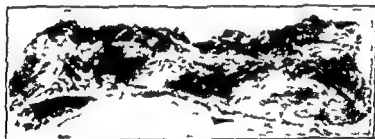


Fig. 319—Photograph of the pancreas from a case of diabetes in a middle-aged person. The islets of Langerhans are diminished in size and number.

**Psychosomatic Factors**—There is scant if any evidence that emotional disturbances play any role in the etiology of diabetes per se. On the other hand, such conditions may act on the pancreas to reduce insulin production or even on the pituitary to increase the diabetogenic hormone. There is ample evidence to indicate that such traumas increase the severity of the diabetic state and that larger amounts of insulin may be required during the period of their operation. It would not be surprising therefore if a latent diabetic state became florid under such conditions and might be accused of being a primary etiological cause (see Chapter XVI).

**Pathological Anatomy**—The absence or variability of pathological findings in the pancreas at autopsy has always been a stumbling block in establishing the functional disturbance upon an anatomical basis. The child diabetic who



dies in coma rarely shows much histological alteration in the pancreas unless it be a general collapse of the organ. The middle aged diabetic whose diabetes is secondary to a gallbladder tract infection frequently shows marked fibrosis with extensive loss of acinar and islet tissue (and sometimes considerable small round cell infiltration). Such cases have had repeated attacks of sub acute pancreatitis. In the aged diabetic the commonest alteration is a total atrophy of the pancreas with little relative alteration in either acinar or islet structure. There are usually mild glides of interstitial sclerosis.

An important contribution that has led to a changing conception of pancreatic pathology was the proof that the islands were capable of regeneration. Previously the pancreas in the diabetic state was viewed as an organ not capable of regenerative capacity but slowly undergoing degenerative changes.

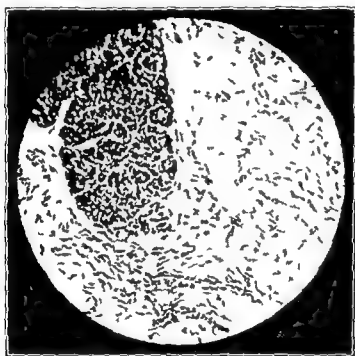


Fig 30—Histograph of a micro section of the pancreas in Fig 319 showing extensive fibrotic replacement of pancreatic tissue

Recently a more labile conception has come to the fore, which views the changes as a result of the balance between regenerative and degenerative forces. With this conception one could imagine a toxic factor acting through out the history of the disease leading to degrees of hyaline degeneration and ultimate fibrosis with loss of function of the islands of Langerhans. Antagonistic to this the regenerative capacity of the organ may result in the formation of new islet tissue. Since its regenerative capacity is so slow one would not expect to find active evidence of the same. The course of the disease is ultimately determined by the balance between these two forces. This conception explains best the pathological alterations found in the elderly diabetics. In many young diabetics one would have to accept the hypothesis that function

can be greatly suppressed without histological alteration. In the middle aged diabetics, usually secondary to gallbladder tract infections, there is a chronic pancreatitis due to an inflammatory reaction initiated and in some cases maintained, by bacterial or chemical causes. Normal bile when injected under low pressure into the pancreatic duct may produce a mild but transient edema and round celled infiltration about the ducts. If infected bile is similarly injected, there is set up an intense necrosis. It has not been proved whether this is due directly to the bacteria or their toxin, or to some chemical change which they have produced in the bile.

**Pathological Physiology**—Since the diagnosis of diabetes mellitus is established by demonstrating that the concentration of blood glucose is excessively high it seems logical to discuss the disturbances in carbohydrate metabolism which exist in this disease from the point of view of those factors which regulate or alter the blood glucose level.

**Blood Glucose**—Normally the concentration of glucose in the blood is maintained within narrow limits. The regulation of this normal level is complicated and is dependent on the normal activity of the gastrointestinal tract, liver, and the endocrine glands particularly the pancreas, anterior pituitary and adrenal cortex.

At any given time the level of blood glucose will depend on the rate at which glucose enters the blood stream and the rate at which it is removed. Stated in a different way it may be said that the blood glucose level is a balance between the rate of its formation and the rate of its utilization. In the fasting state these are so adjusted that the glucose concentration is normally 80 to 100 mg. per 100 cc. During periods when carbohydrate is being absorbed from the gastrointestinal tract the blood glucose concentration will rise. Since the rate of carbohydrate absorption from the intestine is essentially independent of the amount ingested and the mechanisms for the removal of glucose from the blood stream are very efficient the blood sugar concentration rarely reaches a level higher than 140 to 160 mg. per 100 cc. in the normal individual. This peak concentration is usually attained 30 to 60 minutes after the meal. The blood glucose is usually back to the fasting level in 120 to 150 minutes.

In the fasting state in normal individuals the arterial and venous blood sugars are practically the same. After eating a spread develops between the two greatest at the peak values and gradually declining to the postabsorptive state. The difference is due to the removal of glucose from the capillary blood and at the peak values may amount to 60 mg. per 100 cc. The mild diabetic shows practically the same arteriovenous difference as the normal. The more severe the diabetes the less is the difference due to the failure to remove glucose from the capillary blood. This is best shown in the digestive period. Absence of difference in the digestive period is strong evidence of a diabetic state.

**Hyperglycemia**—Since the level of blood glucose is dependent on the rate of its formation and on the rate of its utilization hyperglycemia may be due to overproduction of glucose or to its underutilization or to a combination of the two.

Glucose is utilized in three principal ways (1) oxidation to carbon dioxide and water (2) conversion to liver and muscle glycogen and (3) conversion to fat. The oxidation of glucose is enhanced by insulin while it is inhibited by the carbohydrate active hormones of the anterior pituitary gland and the adrenal cortex. Insulin also enhances the conversion of glucose to glycogen and fat.

In the postabsorptive state glucose is formed from liver glycogen and from noncarbohydrate sources, notably protein and the glycerol of fat by a process known as gluconeogenesis. Insulin inhibits gluconeogenesis while the anterior pituitary and adrenal cortical hormones stimulate it.

It is apparent then that the hyperglycemia associated with acromegaly and Cushing's syndrome is due to both overproduction and underutilization of glucose. In the majority of patients it is likely that the latter mechanism is the more important one.

Since insulin enhances the utilization of glucose and inhibits its production the hyperglycemia associated with insulin deficiency could be due to either or both of these mechanisms. At present the evidence favors the mechanism of underutilization. This also appears to be the case in those patients with diabetes mellitus of unknown etiology.

By virtue of diminished utilization of glucose the blood glucose will reach a higher level in a patient with diabetes mellitus than in a normal individual after the ingestion of carbohydrate. If immediately following a meal the venous blood glucose exceeds 160 mg. per 100 c.c. a state of hyperglycemia may be said to exist. If the underutilization is severe enough the blood sugar will be elevated in the fasting state as well. Values of 100 to 120 mg. are of doubtful significance while a concentration of more than 120 mg. per 100 c.c. of blood is usually considered to signify hyperglycemia.

### The Glucose Threshold in Diabetes —

**Glycosuria** — Glycosuria is one of the important consequences of hyperglycemia since it is responsible for many of the symptoms and signs of the disease. In addition the demonstration that glucose is present in the urine is often the first indication that the patient may have diabetes mellitus. The mechanism of the excretion of glucose in the urine has been elucidated through the researches of Richards.

It would seem to be well established that the glomerular fluid is a mechanical filtrate through Bowman's capsule from the capillary blood and that it contains glucose in the same percentage concentration as the blood in the afferent vessel coming to the glomerulus. As this glomerular fluid passes down the convoluted tubules its glucose is reabsorbed. Glycosuria will occur when the amount of glucose presented to the kidney tubules for reabsorption exceeds their reabsorptive capacity. The amount of glucose presented to the kidney tubules will depend on the plasma arterial concentration of glucose and the volume of glomerular filtrate formed. In the normal individual the maximal amount of glucose which can be reabsorbed in one minute is 350 mg. In Fig. 521 it will be seen that when the blood glucose level reaches 300 mg. per 100 c.c. with a normal rate of glomerular filtration the glucose load to the kidney becomes 390 mg. in one minute. Since the maximal reabsorptive

capacity is 350 mg., the patient will excrete 40 mg. of glucose in the urine in one minute. It is really incorrect to refer to glycosuria in terms of 'renal threshold' because this implies that the occurrence of glycosuria is only dependent on the blood glucose concentration. From the discussion above, it is apparent that at least two other factors are important namely, the rate of glomerular filtration and the tubular reabsorptive capacity for glucose. However the term is firmly entrenched in the literature of diabetes and will be retained in the discussion which follows.

It can be demonstrated by the most sensitive method of analysis that the normal urine contains a trace of glucose, indicating that this small amount escape reabsorption. This 'glycosis' varies from 100 to 900 m $\mu$  of glucose per day and its percentage concentration is not great enough for the alkaline copper solutions to detect it (Benedict's, Fehling's, or Haines' solutions). The diabetic's glucose threshold has the same mechanism of action and the glycosuria that is present is dependent *in toto* upon the elevation of the blood sugar above the threshold. This threshold level is usually considered to vary from 160 to 180 mg. per cent for venous blood. The glucose threshold may be lower or higher than the average normal. On the low side one sees all levels finally merging into those found in renal glycosuria. The author has followed a case for over ten years with a constant threshold of 70 mg. per cent. It is also well established that the threshold may be raised. This elevation occurs in cases of long standing diabetes and especially in those with a progressive arteriosclerosis. Venous blood sugar values of 300 mg. per cent without glycosuria are not rare. The finding of a low threshold does not rule out diabetes. The diabetic state is quite independent of the threshold. The lower the threshold the greater the percentage excretion of glucose in the urine provided the urinary volume and the level of hyperglycemia are relatively constant. Many diabetics have a lowered threshold (120 to 150 mg. per cent venous blood) which is only discovered after the hyperglycemia has been controlled by treatment. If a raised glucose threshold in the kidneys is present the absence of glycosuria may fail to indicate the degree of hyperglycemia.

In Fig. 321 there is a schematic representation of the mechanism of the so called 'raised' and 'lowered' threshold. In diabetic patients with renal arteriosclerosis because of a diminished rate of formation of glomerular filtrate the glucose load presented to the kidney may be less than the tubular reabsorptive capacity in spite of an elevated blood glucose concentration. Therefore glycosuria may not occur even when the blood glucose is 500 mg. per 100 cc. In patients with renal glycosuria on the other hand the glucose load is normal 150 m $\mu$  in the example shown but the ability of the tubules to reabsorb glucose is impaired and as a consequence glycosuria occurs in the presence of a normal blood glucose concentration. Thus if the tubular reabsorptive capacity is decreased to 80 m $\mu$  there would be a glycosuria of 50 mg. in one minute.

The determination of the glucose threshold in the kidney can only be made upon the venous blood during the fasting state. This is essential because the threshold is an index of the arterial blood sugar level and only in the fasting state are they the same. If there is glycosuria in a controlled hourly

specimen taken in the early morning, the urine and venous blood sugar can be followed at hourly intervals until there is no glycosuria. If there is no glycosuria in the fasting urine it is necessary to use capillary or arterial blood to obtain the true threshold. Arterial or capillary blood sugars followed at half hour intervals and coordinated with corresponding urine samples after the administration of 50 grams of glucose by mouth will reveal the threshold. Ideally the proper way to determine whether a low or high 'threshold' exists is to measure the exact glucose load presented to the kidney. This involves the measurement of the glomerular filtration rate. An approximation of this can be obtained as suggested by Coleborn by estimating the urea clearance. It has been claimed that there is a difference between the threshold with rising and falling blood sugars. This is not demonstrable when judged from capillary blood values. This confusion has arisen by attempting to judge thresholds using venous blood after the administration of glucose by mouth.

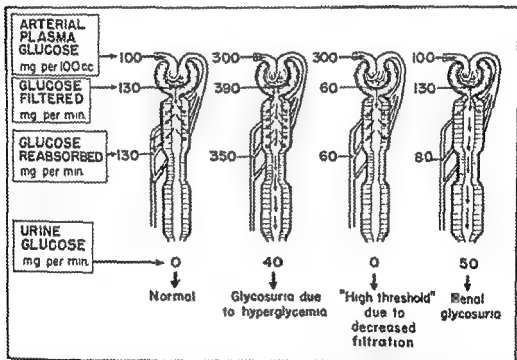


Fig. 31.—(Curtis, A. C. Corlies, Cleveland Clinic Quarterly, October, 1948.)

**Relationship of Carbohydrate and Fat Metabolism**—The tissues prefer to oxidize carbohydrate rather than fat. If the former capacity is impaired a greater proportion of the total calories produced will be derived from fat oxidation. If fat oxidation is complete the end products are  $\text{CO}_2$  and  $\text{H}_2\text{O}$ . If incomplete the ketone bodies,  $\beta$ -hydroxybutyric acid ( $\text{CH}_3\text{-CHOH-CH}_2\text{-COOH}$ ), acetoacetic acid ( $\text{CH}_3\text{-CO-CH}_2\text{-COOH}$ ), and acetone ( $\text{CH}_3\text{-CO-CH}_3$ ) accumulate in the blood and extracellular lymph and a type of acidosis called ketosis results. Probably these ketone bodies are derived from butyric acid.

( $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-COOH}$ ), a 4 carbon atom molecule in the normal oxidative catabolism of the higher fatty acids. The accumulation of ketone bodies in the blood of the inadequately treated severe diabetic is apparently the result of an overproduction of ketone bodies rather than to their diminished utilization. The ketone bodies are formed in the liver and although the precise reason for their overproduction in the diabetic patient is not known, it is likely that the depletion of liver glycogen and the infiltration with fat is responsible for the rapid breakdown of fatty acids into ketone bodies. Ketone bodies can also be derived from certain of the amino acids. Any substances capable of yielding these ketone bodies are called ketogenic. Glucose, derived from carbohydrate, or from certain amino acids of protein, or from the glycerol of neutral fat is said to be antiketogenic. Shaffer has attempted to develop a ratio of ketogenic to antiketogenic substances which, if the tissues exceed in their oxidative functions, would result in a mild ketosis. He stated his ratio to be 2 molecules of keto<sub>g</sub>enic acid to 1 of glucose. Later a ratio of 1 molecule of keto<sub>g</sub>enic acid to 1 of glucose has been shown to be more nearly correct. These ratios are influenced by many factors. The child and pregnant woman have lower ratios than the adult. Further, the tissues of an individual can acquire a greater capacity to oxidize fatty acids, while less glucose is oxidized without ketonuria. With carbohydrate diets containing 150 grams or more, there is no danger of ketonuria provided the carbohydrate ingested is oxidized.

In severe diabetes and especially in diabetic coma marked degrees of lipemia may be present. This can be diagnosed by examination of the fundi or by withdrawal of a sample of blood. Upon standing a cream-like layer separates out above the red blood cells which are rapidly sedimented. Values of 12 to 13 per cent of total lipid concentration in the blood have been reported (normal 0.5 to 0.7 per cent). The cause of this lipemia is related to an increased fat transport via the blood stream, and is always associated in diabetes mellitus with hyperglycemia. With control of the diabetic state it rapidly disappears.

Cholesterol is one of the body lipoids but not a true fat. Very little is known about its exact intermediary metabolism. Its source is the food where it is closely allied to neutral fat. Internal organs meats eggs and butter contain the highest percentages. Uncontrolled diabetic states with hyperglycemia usually have hypercholesterolemia (normal plasma cholesterol 150 to 250 mg. per cent). Values of 500 mg. per cent are not uncommon while in coma figures ranging from 500 to 700 mg. per cent may be present. With establishment of control the cholesterol falls much slower than the blood sugar and when it remains persistently elevated the prognosis is poor. Joslin has found that low blood cholesterols of 90 mg. per cent or under are of more serious prognostic significance than high values.

Great interest is being taken in the relationship of persistent hypercholesterolemia, and the development of arteriosclerosis. Certain authors have been of the opinion that high fat diets which frequently are associated with elevated blood cholesterol tend to produce arteriosclerosis. With the intro

duction of the low fat high carbohydrate diet there has followed a very definite drop in the average of the blood cholesterol

**Relationship of Carbohydrate and Protein Metabolism**—Carbohydrate is the greatest sparer of protein oxidation. By high carbohydrate feeding in normal persons the protein oxidized can be reduced to a minimum (about 19 grams per 24 hours). Provided sufficient carbohydrate is available muscular work is performed at the expense of carbohydrate the protein metabolism remaining unchanged. The diabetic having an impaired ability to oxidize carbohydrate calls upon his endogenous protein to supply needed calories. This call is greatest in the severe cases and especially if fat oxidation is incomplete resulting in a ketosis. The degree of tissue destruction occurring can be accurately determined by the nitrogen excreted in the urine and feces due allowance being made for the exogenous nitrogen in the food (6.25 grams of protein yield 1 gram nitrogen). Loss of weight is rapid where tissue protein destruction is pronounced. Insulin increases the ability of the diabetic to oxidize glucose and permits the protein metabolism to return to normal.

**Insulin and Its Action**—In 1921 Banting and Best with the assistance of Collip working in Macleod's laboratory in Toronto prepared an active pancreatic extract which was capable of lowering the blood sugar. This substance was named insulin. It was not until 1925 that it was isolated in crystalline form by Abel and Gerling. The chemical formula  $C_{41}H_{58}N_{11}S$  has been assigned to it. Its content of tyrosine, arginine and histidine is high, and it contains a sulphur compound similar to cystine. It is capable of forming salts with acids. Insulin is found in practically all body organs especially the pancreas and muscles but the yield per gram of material is greatest from the pancreas and its commercial preparation is limited to extraction from this organ.

The normal individual is constantly receiving a supply of insulin from the pancreas. It is carried by the blood stream to all nucleated cells of the tissues. There it plays an essential part in the storage of glucose as glycogen and the oxidation of glycogen. Without insulin the oxidation of glucose in the muscles may be practically reduced to zero. Evidence would indicate that the tissues contain some unknown factor which is essential for the oxidation of glucose since *in vitro* insulin will not oxidize glucose even in the presence of oxygenated blood. Insulin will also restore the normal spread between the arterial and venous blood sugars absent in the severe diabetic. This would indicate greater glucose removal from the capillary blood. The hormones of other ductless glands (pituitrin, thyroxin and adrenalin) exert a direct or indirect antagonistic action to insulin the resulting blood sugar level being a balance between the two forces.

Insulin is available for clinical use in varying strengths and is standardized in units. One clinical unit is one third of the amount of insulin necessary to lower the blood sugar of a 2 kilogram rabbit kept under standard feeding conditions to the convulsion level. The amount of glucose that one unit of insulin will oxidize varies inversely as the severity of the diabetic state. Roughly one unit of insulin will burn from 1 to 6 grams of carbohydrate.

**Symptoms and Signs**—The concept of the clinical pattern of diabetes has changed radically in the last thirty years. This has been due almost entirely to a ready method of determining the blood sugar. In fact this statement is equally applicable to diagnosis and to treatment. Before such a test was available it was practically only those cases with the florid symptoms of thirst, increased appetite, polyuria, and weight loss with accompanying glycosuria that were so diagnosed. As we know now, a great majority of diabetics in the upper age brackets do not have these symptoms and were therefore overlooked in spite of the fact that glycosuria was present, or, as this was often intermittent or varied considerably from time to time, its significance was not sufficiently

ROYAL VICTORIA HOSPITAL  
MAY 26, 1924

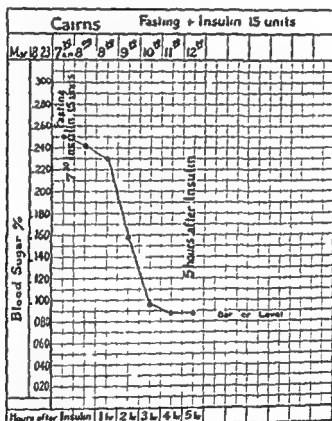


Chart XXIV The effect of insulin upon the blood sugar in the fasting state

appreciated. There is no doubt that there has been a steady increase in the diabetic death rate during the present century. But this may not altogether be accounted for by an actual increase in the disease but to some extent by better means of diagnosis and the appreciation that diabetes may be symptomless.

**Symptoms**—**Polyuria**—The first complaint in the classical symptomatology of diabetes mellitus is usually polyuria. The detailed causation for this has been the subject of considerable controversy. It is therefore important to trace the sequence of events backwards from this point. The urine is clear in color with high specific gravity in proportion to the amount of its glucose content and also in amounts parallel to the latter. The volume may amount



to 5 or 10 or more liters per 24 hours the larger portion being passed in the daytime. In the classical cases this polyuria is in proportion roughly to the degree of hyperglycemia. It is obvious that with a high blood sugar the amount of glucose in the glomerular filtrate will be conspicuously increased. As this is a threshold substance it would be expected that the amount of glucose reabsorbed by the tubules would be considerable but there is probably a limit beyond which this vital function may be ineffective in consideration of the high glucose content of the plasma on the other side of the tubular membrane. Therefore the tubular content cannot be deprived of glucose to the almost complete extent as occurs under normal conditions. Hence the glycosuria! But yet there is an excess of water left in the tubular content or urine. One could postulate that the amount of urine should be reduced in order that the glucose isotonicity of the tubular vessel in blood content would be maintained as nearly to a normal level as possible. This would be in almost vain attempt in the florid cases or episodes in this disease (see below). On the other hand one might speculate that the pituitary or midbrain centers are sensitive to hyperglycemia and so affect the diuretic factor as to increase its influence on renal tubular function. There is another possible explanation which is a positive one related to the first but contrary postulate above. This is that the tubular blood supply is saturated with glucose that the tubular content or urine withdraws water into the tubules since the concentration of glucose there is greater than in the blood stream or on the other hand prevents its transference inwardly and so the polyuria. This matter has not been clarified by experimental means. For instance dogs have been continuously infused with glucose solutions producing a glycosmia of 12 to 13 per cent. At such levels 1 gram of glucose carries with it only 6 to 6 cc. of water. Frequently a diabetic excretes as much as 12 cc. or more of water for each gram of glucose. But it must be appreciated that such dogs are not diabetic and more nearly approach the normal person who after a heavy carbohydrate meal easily rid himself of a small overflow of carbohydrate or the person with a low glucose renal threshold who passes glucose in the urine with a normal blood glucose level and no diuresis. But there is no insulin deficiency and this factor has not yet been sufficiently explored to reach a conclusion as to the relative importance of a high glucose glomerular filtrate with a normal systemic blood sugar or a high systemic blood sugar and a normal glomerular filtrate but an impaired tubular function. The last would not seem to be of much importance in the present concept as in the nephrotic stage of glomerulonephritis in lower nephron nephrosis etc. (see Chapter XVIII) glycosmia is not a feature.

The fact remains from a practical clinical standpoint that in the florid pattern of diabetes in children young adults and occasionally in the upper decades polyuria may be the presenting symptom but in many of the latter unfortunately it is not sufficient to require the patient to seek professional advice and so the diabetic state passes unnoticed for an indefinite time.

**POLADIPSIA.** Thirst in the classical pattern of diabetes is the second most frequent symptom. There has been much argument and speculation as to its causation. Since glucose is a freely diffusible substance its concentration is

**Symptoms and Signs**—The concept of the clinical pattern of diabetes has changed radically in the last thirty years. This has been due almost entirely to a ready method of determining the blood sugar. In fact this statement is equally applicable to diagnosis and to treatment. Before such a test was available, it was practically only those cases with the florid symptoms of thirst, increased appetite, polyuria and weight loss with accompanying glycosuria that were so diagnosed. As we know now, a great majority of diabetics in the upper social brackets do not have these symptoms and were therefore overlooked in spite of the fact that glycosuria was present or is thus it is often intermittent or varied considerably from time to time. Its significance was not sufficiently

# ROYAL VICTORIA HOSPITAL

1904-5

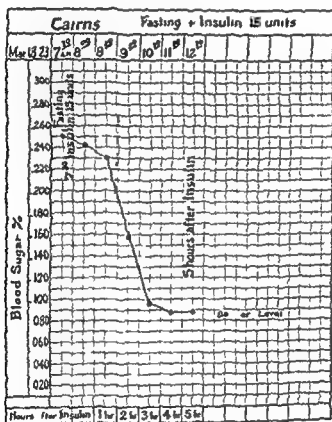


Chart XXIV—The effect of Insulin upon the blood sugar in the fasting state

appreciated. There is no doubt that there has been a steady increase in the diabetic death rate during the present century. But this may not altogether be accounted for by an actual increase in the disease but to some extent by better means of diagnosis and the appreciation that diabetes may be symptomless.

**Symptoms**—**POLYURIA** The first complaint in the classical symptomatology of diabetes mellitus is usually polyuria. The detailed causation for this has been the subject of considerable controversy. It is therefore important to trace the sequence of events backwards from this point. The urine is clear in color with high specific gravity in proportion to the amount of its glucose content and also in amounts parallel to the latter. The volume may amount

to 5 or 10 or more liters per 24 hours the larger portion being passed in the daytime. In the classical cases this polyuria is in proportion roughly to the degree of hyperglycemia. It is obvious that with a high blood sugar the amount of glucose in the glomerular filtrate will be conspicuously increased. As this is a threshold substance it would be expected that the amount of glucose reabsorbed by the tubules would be considerable but there is probably a limit beyond which this vital function may be ineffective in consideration of the high glucose content of the plasma on the other side of the tubular membrane. Therefore the tubular content cannot be deprived of glucose to the almost complete extent as occurs under normal conditions. Hence the glycosuria! But yet there is an excess of water left in the tubular content or urine. One could postulate that the amount of urine should be reduced in order that the glucose isotonicity of the tubular vascular blood content would be maintained as nearly to a normal level as possible. This would be an almost vain attempt in the florid cases or episodes in this disease (see below). On the other hand one might speculate that the pituitary or midbrain centers are sensitive to hyperglycosuria and so affect the diuretic factor as to increase its influence on renal tubular function. There is another possible explanation which is a positive one related to the first but contrary postulate above. This is that the tubular blood supply is saturated with glucose that the tubular content or urine withdraws water into the tubules since the concentration of glucose there is greater than in the blood stream or on the other hand prevents its transference inward and so the polyuria. This matter has not been clarified by experimental means. For instance dogs have been continuously infused with glucose solutions producing a glycosuria of 12 to 13 per cent. At such levels 1 gram of glucose carries with it only 6 to 8 cc of water. Frequently a diabetic excretes as much as 12 cc or more of water for each gram of glucose. But it must be appreciated that such dogs are not diabetic and more nearly approach the normal person who after a heavy carbohydrate meal easily rids himself of a small overflow of carbohydrate or the person with a low glucose renal threshold who passes glucose in the urine with a normal blood glucose level and no diabetes. But there is no insulin deficiency and this factor has not yet been sufficiently explored to reach a conclusion as to the relative importance of a high glucose glomerular filtrate with a normal systemic blood sugar or a high systemic blood sugar and a normal glomerular filtrate but an impaired tubular function. The last would not seem to be of much importance in the present concept as in the nephrotic stage of glomerulonephritis in lower nephron nephrosis etc (see Chapter XVIII) glycosuria is not a feature.

The fact remains from a practical clinical standpoint that in the florid pattern of diabetes in children, young adults and occasionally in the upper decades polyuria may be the predominant symptom but in many of the latter unfortunately it is not sufficient to require the patient to seek professional advice and so the diabetic state passes unnoticed for an indefinite time.

**POLYDIPSIA:** Thirst in the classical pattern of diabetes is the second most frequent symptom. There has been much argument and speculation as to its causation. Since glucose is a freely diffusible substance its concentration is

the same in the extracellular tissue fluids as in the plasma. It has been postulated that there is a shift of water from the cells to the body fluids, resulting in tissue dehydration. But this still remains to be proved. If one takes the erythrocytes as a representative while the glucose content is in equilibrium with the plasma, there is no detectable difference in the formation or function under these conditions. Therefore, it is hard to believe that a fundamental shift of the cellular water balance leading to occult cellular dehydration is the cause of the thirst and consequent polydipsia. It seems much more logical to postulate for the present that this is a direct result of the polyuria. It is a well known fact that pronounced hyperglycemia and glycosuria without polyuria can be present without thirst or polydipsia.

**POLYPHAGIA.** In the classical clinical pattern of diabetes, polyphagia or hunger is a prominent symptom. The cause of this is not far to seek. The first action of insulin is to act on the liver in the storage of glucose as glycogen. This in turn on demand is released for use by the muscles and all other functioning organs. In the second place, insulin is of essential importance in the utilization by the tissues of the released glucose from liver glycogen. Therefore if the ingested glucose cannot be stored and utilized other sources such as proteins and fat within the body are called upon to supply the demand which in turn are utilizable after a normal manner. So in conformity with a common law of deprivation there is an increased desire on the part of the organism for an unusual demand. It is of importance to note in this regard that the diabetic craves carbohydrate in a concentrated form which will be seen later to be one of the hazards of therapy in uncontrollable cases. So the polyphagia or gluttony of this type of diabetes is due to a failure of storage and utilization of carbohydrate in which manner a large proportion of the caloric value of ordinary meals is lost and is manifested by the degree of glycosuria.

**LOSS OF WEIGHT.** This might be considered a secondary complaint in the symptomatology of classical diabetes and in the whole picture it is a paradox. It would seem obvious that the loss of weight is primarily due to inability of the liver to store glycogen and the tissues to utilize it. If appreciable potential calories are excreted in the urine in the form of glucose the tissue will oxidize an equivalent amount derived from fat and protein. If the tissue protein is oxidized in a marked degree the weight loss will be rapid. A calculation will show that this is about eleven times more rapid when an equivalent number of calories is being derived from protein than from fat. The weight loss referable to dehydration is of minor importance.

It has been mentioned above that obesity is often a precursor to diabetes particularly in the older age groups. This may remain present or even increase over the years if the caloric intake is excessive. Herein lies an unexplained paradox. On the other hand some patients lose weight and parallel with this the diabetic process improves.

Other symptoms of less frequent occurrence are pruritus vulvæ, weakness and constipation. The pruritus may be generalized and is usually associated with dehydration and heavy glycosuria. Drying of the urine on the vulva may cause a local irritation which is not uncommonly the symptom

for which the patient seeks medical aid. Pruritus vulvæ of this type will disappear promptly when the glycosuria has been controlled. More rarely the pruritus vulvæ is associated with a local mycotic infection. Possibly the urinary glucose serves as a favorable culture media. Such cases require special treatment. Weakness is a symptom of diabetes in proportion to the loss of weight. Constipation is probably a matter of withdrawal of water from the intestinal tract. Very few controlled diabetics eating vegetables and fruits are constipated.

For years it was considered usual for patients with diabetes to complain of varying degrees of pain in their limbs and to show signs of neuritis. The hyperglycemia was blamed as the cause. Recent investigations have suggested the probability of a vitamin B<sub>1</sub> deficiency. A large percentage of diabetics with neuritis have partial or complete achlorhydria which may have an etiological relationship to the vitamin deficiency.

**Signs**—The physical examination of a diabetic patient is completely void of any signs diagnostic of the disease. However one finds varying degrees of dehydration and dryness of the skin and minor skin infections are common. Evidence of weight loss may be present. The neurological examination may show absence of the prepatellar tendon reflex in almost 50 per cent of the untreated cases. This sign is rare in the young.

**Clinical Classification**—The fact that the diabetic state is not fixed makes it very difficult to classify in any satisfactory way. The divisions, mild, moderate and severe as judged by the patient's ability to oxidize glucose are probably the most satisfactory.

Mild cases are those not requiring insulin but are satisfactorily controlled by diet alone. Moderate cases require 30 units or less of insulin per 24 hours while severe cases demand more than 30 units. Proper diabetic control means approximate freedom from glycosuria, absence of ketonuria and a diet sufficient in calories to maintain weight. One must not forget that a case may change from one group to another as a loss or gain of tolerance takes place. This fluctuation of tolerance partly rests in the hands of the doctor and can be influenced greatly by proper diet, insulin dosage and exercise. In the main diabetes in childhood unless carefully supervised tends to become severe while after 60 years of age the disease is usually fundamentally mild.

On the other hand diabetes may be classified as insulin sensitive and insulin insensitive. In the first class there would be included all those cases of what might be called idiopathic diabetes which readily respond to insulin therapy and so are supposed to be due to a primary deficiency of the pancreatic internal secretion. The second group do not respond to insulin and the cause can usually be traced to an abnormality in some other system or organ (see page 810).

### Complications

**Cardiovascular Disease**—The etiology of arteriosclerosis is unknown. Its incidence at the onset of diabetes varies directly as the age of the patient. When not present at the onset it develops earlier in diabetics than in other patients. It is rare to see a middle aged patient who has had diabetes for ten years

without some degree of calcification of the arteries. Even with the onset of diabetes in childhood a ray signs of calcification may appear in the third decade. The author has seen a diabetic, male, aged 27 years, with an eleven year history, who had extreme systemic arteriosclerosis with gangrene of one



Fig 3 —X ray of the foot in a case of diabetes showing calcification of the arteries

toe. The present evidence would indicate that excess lipid in the blood contributes to the production of this arterial lesion. Virchow showed that the intima of the larger arteries contained excess lipid in arteriosclerosis. This lipid is a cholesterol ester which is later bound to calcium. Any state that results in an excess blood lipid concentration such as obesity or a high fat diet, would tend prematurely to develop this arterial lesion.

There is little fundamental difference between the arteriosclerosis in diabetics and in nondiabetics. Our experience has been that the arteriosclerotic process expresses itself as a degenerative change in the media with hyaline fusion and often calcareous deposits. There is also marked intimal thickening and narrowing of the lumen with frequent occlusion by thrombosis. The medial change corresponds to the so called Monlberg type of arteriosclerosis, but this is believed to be due to the size of the vessel involved rather than to any essential difference from ordinary arteriosclerosis.

**Gangrene**—Gangrene of the lower extremities is a common complication in diabetics. It usually involves one or more toes but may develop in the tarsus as well. It is due to death of tissue from lack of blood supply. It is dry or moist according to the presence of secondary infection. The so called "diabetic gangrene" differs from nondiabetic gangrene only in its tendency to infection and rapidity of spread. As it spreads the surrounding tissues become reddened, edematous and streaks of lymphangitis appear. Frequently a small infection at the corner of a nail or under a corn or callus is the initiating factor for the onset of gangrene. Given the two conditions hyperglycemia and impaired circulation gangrene is a potential danger.

The lower extremity that has a grossly impaired circulation will show marked atrophy of the skin of the foot with loss of subcutaneous tissue. Shiny skin is stretched over the bones like a mummy. Pulsation in the dorsalis pedis and posterior tibial arteries cannot be palpated and the x ray may show varying degrees of calcification of the vessel walls (Fig. 322). It is possible to have poor circulation with no sign of calcification while on the contrary there may be good circulation with pronounced calcification of the arteries as shown by x ray. Surface temperature measurements after a spinal anesthetic or lumbar sympathetic block and the histamine flare test may be of value in special cases. The most important single criterion of the efficiency of the circulation upon which depends the capacity of a gangrenous area to heal is palpable pulsation in the dorsalis pedis vessel. Next in significance is the state of atrophy of the skin and subcutaneous tissues. The degree of calcification revealed by x ray is an unreliable guide.

**Arteriosclerosis of Other Organs**—Next in importance to involvement of the legs is sclerosis of the coronary arteries leading to myocardial infarction. The retinal vessels show changes rather early progressing to hemorrhages and exudate the so called "diabetic retinitis".

To any one who follows diabetics over many years a striking feature is the large number who develop a progressive failure of renal function due to vascular changes in the kidneys. The diabetic state frequently becomes milder and there is a parallel depreciation of renal function. Death takes place from uremia. This has now been identified with intercapillary glomerular sclerosis (see Chapter XVIII). Cerebral thrombosis and cerebral hemorrhage are the causes of death in many with advanced cerebral arteriosclerosis.

**Infections**—Some think that the diabetic is susceptible to infections on account of hyperglycemia. Clinically it is our conviction that the controlled diabetic has not an increased susceptibility to infection. The healing of

cises recover. Likewise pulmonary abscess can be given a good prognosis if satisfactory drainage can be established.

**Diabetes and Pulmonary Tuberculosis**—Before insulin (1922) the prognosis of the diabetic with active pulmonary tuberculosis was extremely grave. Today the situation is not hopeless. A great deal depends upon the intelligence and the care of both the patient and the doctor. An illustration of what can be accomplished in some cases at least is that of a young woman who is now 40 years of age in whom diabetes was first recognized in 1919. Due to extreme conscientiousness on her part, she survived on a weighed diet to receive insulin in 1922. Subsequently her level of nutrition was built up to normal standards. For a time she became careless with her diabetic control and during this period she contracted pulmonary tuberculosis. In 1933 she had an active pulmonary lesion with positive sputum, and the x ray showed conspicuous involvement of the left upper lobe. A diet of protein 70 gm, fat 50 gm, and carbohydrate 325 gm required 96 units of insulin per day. Partial collapse of the affected lung was maintained for twelve months. The sputum became negative and in one year all clinical and x ray evidence of the activity in the pulmonary lesion had disappeared. Today she is enjoying almost a normal life with a diet of protein 70 gm, fat 50 gm, and carbohydrate 275 gm, and 58 units of insulin a day.

There is little doubt that the diabetic is more susceptible to a tuberculous infection becoming active than the nondiabetic. This susceptibility is not great in the controlled diabetic, but is very appreciable in the uncontrolled case. The juvenile diabetics are much more susceptible than the adults. Great care should be exercised over diabetic children to avoid all contact with open tuberculosis and routine x rays should be taken of their lungs at yearly intervals. The use of BCG vaccine in those children who are Mantoux negative should be seriously considered.

### Acidosis (Ketosis) —

**Nature of Chemical Disturbance**—Diabetic acidosis is due to the incomplete oxidation of fatty acids. When this oxidation reaches the stage of the 4 carbon atom butyric acid the two ketone acids  $\beta$  hydroxybutyric acid and acetoacetic acid are formed from which acetone is derived. These ketone acids pass into the blood stream and are converted into sodium salts at the expense of the  $\text{NaHCO}_3$  present. Thus as their formation increases there is a greater exhaustion of the main base reserve. With the formation of the salt  $\text{NaHCO}_3$  is broken down liberating  $\text{CO}_2 + \text{H}_2\text{O}$ . The  $\text{CO}_2$  leaves the body via the lungs. If the base reserve is exhausted a shift of the pH of the blood follows and death takes place. Chemically the severity of the acidosis is indicated by the CO capacity of the blood plasma. When treatment is instituted and carbohydrate is oxidized by insulin, the production of these ketone bodies ceases and those that are present are either oxidized or excreted.

	PLASMA CO CAPACITY
Normal	55 to 65 vols %
Mild acidosis	35 to 45 vol %
Moderate acidosis	25 to 35 vol %
Severe acidosis	Below 25 vols %



When oxidized the base sodium is liberated and unites again with  $\text{CO}_2$  to form  $\text{NaHCO}_3$  with the restoration of the base reserve. Many cases of coma will show no alteration of the blood sodium throughout the total period of their recovery.

Recently attention has been directed to the importance of potassium depletion in diabetic coma. In coma there is an excessive phosphaturia which decreases the labile organic phosphates in the blood and tissues. This is further accentuated by the diuresis which results from excessive glucose and fluid therapy. The blood potassium may be reduced to such a degree as to cause muscular paralysis particularly dangerous to respiration and the electrocardiogram will show the typical changes of the S-T complexes associated with hypokalemia.

*Symptoms and Signs*—The symptoms characteristic of severe acidosis are air hunger (Kussmaul), flushed appearance and dry skin. The pulse is rapid and the eyeballs are soft. The tongue is dry and there may be vomiting with at times epigastric pain. A  $\text{CO}_2$  capacity below 16 volumes per cent is usually associated with unconsciousness. The air hunger is characterized by deep and rapid respirations and is the most constant single symptom in a severe ketosis. It is probably due to the stimulation of the carotid body by the fatty acids although it helps to reduce the  $\text{CO}_2$  of the blood by elimination of  $\text{CO}_2$  through respiration. Lipemia and an increase of blood cholesterol may be found during coma but it is usually temporary and has no prognostic significance. Dehydration accounts for the dry skin and dry tongue. The flushed appearance may partly be a matter of increased circulation rate as indicated by the pulse and in part due to a decreased amount of reduced hemoglobin in the venous blood (note its bright red color) due to the increased  $\text{O}_2$  content of the alveolar air brought about by the hyperventilation and also an increased circulation rate. The decreased intraocular tension is due to withdrawal of water from the vitreous. Vomiting is readily relieved by gastric lavage which would indicate a local rather than central cause. The epigastric pain in some cases would appear to be due to a subacute pancreatitis.

The breath of the patient is fruity in odor due in part to acetone. The urine shows glucose, acetoacetic acid and acetone. There is a hyperglycemia and a ketonemia. Children in diabetic coma with vomiting and abdominal pain frequently show great rigidity of the abdominal wall and a marked leucocytosis. Thirty to forty thousand white cells is not unusual and one case occurred in this clinic with 52,000. The leucocytosis is of the polymorphonuclear type and the count rapidly returns to the normal level as the acidosis is cured. These cases are often confused in diagnosis with acute peritoneal infections.

*Effect of Acidosis Upon Carbohydrate Tolerance*—We have never been able to detect any permanent impairment of tolerance following diabetic coma (ketosis). One of our patients with an onset of diabetes at eleven years had thirteen attacks of coma during the first five years of her illness. She is now twenty-six years of age. There was only a very temporary impairment of tolerance following each attack. At no time was her growth arrested and puberty was only slightly delayed.

### Other Complications —

*Gallstones and Gallbladder Disease*—Cholecystitis and cholelithiasis are common findings in the middle aged, obese, diabetic woman. The biliary tract infection usually precedes the appearance of the diabetic state, and is probably the primary cause of it. Infected bile has been proved to be capable of causing a pancreatitis and these diabetics frequently have recurring attacks of subacute pancreatitis. Cholecystitis is potentially more dangerous than cholelithiasis. Provided the diabetic state has not been present for more than three months drainage or removal of the gallbladder as indicated may result in marked improvement of carbohydrate tolerance.



Fig. 3 —Xanthoma diabetorum. (Courtesy of Dr. Philip Frank Staffner. From Sutton and Sutton: *Diabetes of the Skin*.)

*Xanthoma Diabeticorum*—With the use of lower fat and higher carbohydrate diets xanthoma diabeticorum has almost disappeared. The yellowish tubercles which appeared especially in the skin, were composed of fat cells in a connective tissue stroma with a deposit of cholesterol crystals in their centers. They appeared more frequently upon the extensor surfaces at the points of slight trauma or friction. Rarely were they generalized over the whole body. These patients had hyperglycemia, lipemia and marked hypercholesterolemia (500 to 1000 mg. per cent). With diabetic control the tubercles rapidly disappear leaving small whitish scars in the skin. Increase in

the blood cholesterol of the same order is encountered in the nephrotic state but xanthomatosis does not occur

**Cataracts**—Anthony has shown statistically that there is a very significant association of cataracts with diabetes. They were fifteen times as common as expected in the age group between sixty and seventy four and 202 times as great as expected between twenty five and thirty. Cataract in juveniles does occur but it is not common and develops early in the disease.

**Hypertension**—Reference has already been made to the frequency of arteriosclerosis in diabetes mellitus but it does not necessarily follow that the former is the cause of hypertension in this disease. It is generally accepted that hypertension is more common in diabetics than in corresponding age groups of nondiabetics but there are some who do not agree with this. However of the anatomical lesions found at autopsy arteriosclerosis is first and cardiac hypertrophy second. This would seem to bear witness that hypertension is a common complication of diabetes mellitus.

**Intercapillary Glomerulosclerosis**—Reference will be made to this on page 1275. Although this is a comparatively rare condition the relatively high incidence of associated diabetes is significant. This is most common in young persons with diabetes of long duration.

**Retinopathy**—Retinopathy occurring in diabetes has long been recognized by ophthalmologists. In fact they differentiate a distinct type of the lesion associated with this disease. It is significant however that there is commonly but not always hypertension present also that the cause of death in many of these cases is nephritis or cerebral or coronary artery lesions. There is no doubt that the presence of retinopathy is of serious prognostic import at all ages.

### Diagnosis

It has been stated above that diabetes mellitus may be present without exhibiting any symptoms or signs. On the other hand the onset may be sudden and the disease may progress to an advanced stage in a comparatively short time. For the sake of clarity the diagnosis will be considered under three groups.

1 The florid type of case offers little difficulty where the patient complains of any or all of the following—polyuria, thirst, polyphagia, weight loss with abundant glycosuria. A blood sugar curve would confirm the diagnosis. However some of these symptoms may be present in other diseases as in hyperthyroidism or anxiety states with or without glycosuria and to make a definite diagnosis a hyperglycemia of a diabetic character must be present.

2 The accidental finding of a reducing substance in the urine in a routine examination as when seeking insurance offers more difficulty. It is well to determine the exact nature of the reducing substance by fermentation, osazone formation or by the polariscope. If it turns out to be a true glycosuria a blood sugar curve is indicated. This should be done after the patient has been on an adequate diet high in carbohydrate for three days as a low diet over a period of time so affects the liver as to permit a high blood sugar curve to be present. However a fasting blood sugar above 140 mg per cent

is certain evidence of the diabetic state, as all nondiabetic causes of glycosuria have normal fasting blood sugar levels except acromegaly, Cushing's syndrome and pheochromocytoma. If glycosuria is present with a normal fasting blood sugar level hyperthyroidism, acromegaly, Cushing's syndrome, hepatic lesions, intestinal lesions and renal glycosuria must be considered. In all incipient or doubtful cases the glucose time curve is most important and if there is still any uncertainty when this is done with venous blood as is customary, then a curve done with capillary blood after immersion of the arm in hot water may be of the greatest value.

3 In some elderly patients who complain of either an unexplained increase or decrease in weight, furuncles or a cutibacule, or peripheral gangrene (particularly of the toes) but without apparent glycosuria, diabetes should be suspected. As persons in the upper decades often have a high renal threshold for glucose glycosuria may not be present in a single specimen of urine. It is well to control such a possibility with a fasting blood sugar estimation in the first instance and follow it by a blood sugar curve if there be any doubt.

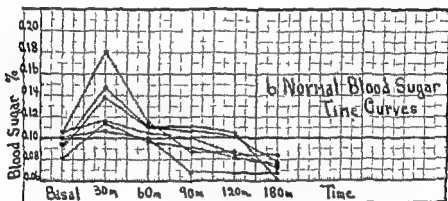


Chart XXX—Six normal blood sugar time curve. Note the closeness of the peak at thirty minutes but the variation in the rate of the prompt return to the basal line and the subsequent drop and fall with the fasting level.

**The Glucose Time Curve**—The glucose time curve is a synchronous observation of the blood sugar and the urine sugar starting in the fasting state and continued over a two to three hour period after the administration of 50 to 100 grams of glucose by mouth. The blood sugar curve so obtained reflects the efficiency of the balance of those forces tending to elevate and those forces tending to lower the blood sugar. Since there is a maximum rate of absorption of glucose from the stomach and upper intestine excess administration of glucose only tends to prolong the absorption period. Fifty grams of glucose give the same blood sugar curve as 100 grams. Most clinics have used the latter amount.

The normal individual shows the peak of the blood sugar rise in thirty minutes with a return to normal in sixty to ninety minutes. Subsequently the blood sugar falls below the fasting value to return to it in the third to the fourth hour. There is no glycosuria. The height of the peak is of little importance provided the drop is precipitous and reaches the fasting level on time. The character of the normal curve is dependent upon an active secretion of insulin which is initiated by the rising blood sugar. This insulin accelerates the storage of glycogen mainly in the liver which more than offsets

absorption. Thus the blood sugar starts to fall and a peak is formed. The rate of fall is largely an index of the rapidity of glycogen storage. The mild hypoglycemic level from the second to the third or fourth hours is due to storage rather "overdoing" itself for a limited period of time. The peak of arterial blood sugar normally ranges from 160 to 200 mg per cent while the venous ranges from 140 to 160 mg per cent.

The diabetic glucose time curve characteristically shows four abnormalities. The more severe the diabetes is (1) the higher the fasting blood sugar, (2) the higher and more delayed the blood sugar peak, (3) the longer the blood sugar takes to return to the fasting level and (4) finally the presence of glycosuria during the period that the arterial blood sugar exceeds the threshold. Only the very mildest diabetics show any hypoglycemic response.

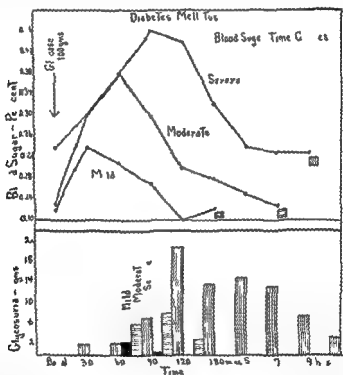


Chart XXXI—(1) Diagram illustrating the effect of varying severity of diabetes on the blood sugar time curve. Note the more severe the diabetes the higher the peak, the more delayed the peak, and the slower the return of the blood sugar to normal.

Undue prolongation of the hyperglycemic phase is usually considered to be more important than the height of the peak. The severe diabetic will show a quantitative relationship between the amount of glucose taken and the degree of hyperglycemia which also controls the glycosuria.

Barring infections and other known diseases which alter the character of the glucose time curve the previous diet of the patient is the most important factor to control. Normal individuals who have been partly depleted of their liver glycogen by a low carbohydrate diet will give a diabetic type of curve. Mild diabetics on similar low carbohydrate diets may give the findings of a severe diabetic. Thus to obtain a result that is the truth there should be no restriction of carbohydrate for at least three days before the test.

The value of the glucose time curve is greatest in differentiating the incipient diabetic. When the venous curve leaves the diagnosis uncertain, a capillary curve will frequently settle it.

**Differentiation from Severe Hypoglycemia**—Acidosis and insulin are both capable of producing coma. Their differentiation is sometimes of critical importance. *Acidosis coma* has typical *air hunger*, soft eyeballs and usually a flushed appearance with dry skin. The breath is fruity and the urine contains sugar and a strongly positive ferric chloride reaction (ketoketotic acid). In *insulin coma* the patient is pale and sweating, there is *no air hunger*, the eyeballs are not soft, twitching and convulsive movements are more common and the urine does not contain ketone bodies. There may be sugar in the urine if the patient has not voided for more than three hours.

### Prognosis

With the advent of insulin the outlook for diabetes has been completely changed. Joslin's experience shows that the average duration of diabetes has been extended from 4.9 years in the Vawter era (1898 to 1914) to 14.1 years in the period 1944 to 1946. In similar periods the average age at death has risen from 44 to 64.5 years. Most diabetics today do not die of this disease but of the resulting complications. Also their general physical condition apart from diabetes plays an important part. The reliability and faithfulness of the patient to follow and the ability of the doctor to direct and carry out a modern system of treatment give the best means of assuring a normal expectation of life. The course of the disease is usually progressive but the rate of this depends upon the degree of control of the process. An increase of insulin requirement is to be looked for in the majority of patients but not necessarily so. In fact in about one third of well controlled patients the insulin requirement may decrease over the years until in some it may be removed altogether. These patients should not be considered as cured but rather that the process is latent and may return to activity during a period of physical or emotional trauma or infection. In the cases of obesity in which there is improvement with weight loss there is usually a recrudescence if the obesity returns.

In children under good control the course and life expectancy in years is even better than in adults and the complications are less serious as to life and well being, until they reach the upper age decades.

At the present time the years of life expectancy at all ages is about two thirds the normal after the disease is first detected. For white persons in the United States aged 10 the expectancy for the normal is 57 more years and for the diabetic forty more; at the age of 65 it is 12 years and for the diabetic 8 years.

The principal primary causes of death in diabetes have greatly changed between 1914 and 1944 as shown below.

	1914 (%)	1944 (%)
Coma	67.8	3.1
Cardiovascular	1.5	61.4
Infections	4.4	7.8
Others	1.3	21.1
	<hr/> 100.0	<hr/> 100.0

### The Objectives and Principles of Treatment

The objectives and principles of the treatment of diabetes mellitus are simple and straightforward. The former may be stated to be threefold: namely, the maintenance of a fairly normal blood sugar level, the maintenance of body weight within a normal range, and the prevention of acidosis and gangrene.

It must be borne in mind that diabetes is a quantitative disturbance of a particular function. In common with other similar diseases this function will deteriorate if exercised beyond its capacity over a prolonged period or if the function is not called into activity. This is particularly true in the former instance if the function is in any way embarrassed. On the contrary, it can be improved many times by putting it at comparative rest and then by gradually making increasing demands the function may largely return toward its normal capacity. It will be outlined below how this may be accomplished in diabetes.

The occurrence of coma is in direct frequency to the severity or degree of impaired carbohydrate storage and utilization. In other words, to the control of the diabetic state is indicated by the hyperglycemia. It has been found also to be roughly parallel to the lipemia and cholestolemia. Therefore to the principle of attempting to improve the carbohydrate metabolism there has been added the reduction of fat in the diet in the hope of avoiding this. Whether such reduction of the lipemia also helps to curtail the formation of acetoacetic and oxybutyric acids is open to question. But there seems little doubt that on a low fat and high carbohydrate diet the diabetic state is more easily controlled.

It has been suggested for many years that hypercholesteremia is a factor in the production of arteriosclerosis. There are certain experimental observations which would support this view. But it must be stated that this is not yet proved. However, even if there be a modicum of evidence in its favor it would seem in the way of wisdom to pay attention to it as arteriosclerosis is at present the principal complication of diabetes mellitus since it is directly or indirectly the cause of most deaths and much disability. There is a close association between impaired circulation and gangrene and the trigger to initiate the latter is very often an incidental infection of the part involved. This is most likely if the diabetic state is not under control. Therefore the meticulous care of the feet to prevent a portal of entry for infection is of the greatest importance.

**Treatment**—Successful treatment of diabetes mellitus necessitates the following of a planned system. There must be complete cooperation on the part of both the doctor and the patient. Before insulin (1922) the principle of undernutrition was stressed. Subsequently, for a time the high fat diet of Newburgh and Marsh was successfully used. Gradually from 1930 a lowering of fat and a raising of carbohydrate have been under way. It was shown that this could be done in isocaloric shifts without changing insulin requirement. Samson, Gejehn and others stressed the value of the high carbohydrate diet but not always was the total calorie content kept low and the hyperglycemia controlled. Thus in the space of a few years we have passed from a low carbohydrate to a high carbohydrate diet from the principle

of resting to that of exercising a weakened function. This is a radical change and has not yet been adopted by many students of diabetes. Some have reached a halfway position, giving from 150 to 200 grams of carbohydrate per day. At the Royal Victoria Hospital for the past fifteen years we have given from 200 to 300 grams of carbohydrate per day, the average being 250 grams. The protein is maintained at  $1\frac{1}{4}$  to 2 grams per kilogram body weight ranging from 70 to 100 grams per day while the fat is usually kept at a level of 50 grams. This is not a high calorie diet. In fact we average almost 200 calories less per day than when using the high fat low carbohydrate diet. Values of protein 70, fat 50, and carbohydrate 250 grams give only 1777 calories.

Common sense and experimental data support the principle of high carbohydrate feeding in diabetes. We know that exercise improves carbohydrate tolerance. It is logical to think that if we wish to strengthen a weakened physiological function, the working of it would be beneficial. Using a muscle strengthens the muscle. Atrophy with impaired function follows disuse. Again the liver that is rich in glycogen handles glucose entering the portal circulation more efficiently. By depriving a normal individual of sugar and starch for a few days the liver glycogen will be so depleted that the glucose time curve will simulate a mild diabetic. Repeated glucose time curves in mild diabetics show a better utilization of carbohydrate with the second dose of glucose. Critics of the low fat high carbohydrate diet have stated that fatigue of insulin production by the pancreas would develop but such has not been the case in our experience. In fact tolerance progressively improves. The success of the diet rests with the low calorie intake which is only possible with restricted fat.

After fifteen years of experience with the low fat high carbohydrate diet as contrasted with the high fat (150 gm) low to medium carbohydrate (60 to 100 gm) diet one can make the following statements:

- 1 The average initial insulin requirement is moderately larger but within three months it is the same or less.
- 2 A progressive improvement of carbohydrate tolerance continues over years. This was not seen with the high fat diet.
- 3 Weight is maintained with fewer total calories (1700 to 1900). This may be explained by a greater water content of the tissues.
- 4 The blood cholesterol averages lower from 150 to 200 mg per cent.
- 5 The incidence of acidosis is much less.
- 6 Infections are tolerated better due to a greater glycogen reserve.
- 7 The tissues have a better healing power.
- 8 There is less necessity for radical amputation in gangrene of the lower extremities.
- 9 There is less weakness in the elderly diabetic.
- 10 No danger from lack of vitamin A has been observed.
- 11 The incidence of dental caries is no greater. This statement is based upon the use of the diet in growing children.
- 12 There is considerable evidence that the onset of arteriosclerosis is delayed.
- 13 The diet is cheaper and is less upsetting to the home.
- 14 No special foods are required.



15 There is no evidence in fifteen years of any fatigue of carbohydrate tolerance

A weighed diet is to be preferred, and should be used with all children and severe diabetics. Calculation in the metric system and the use of gram scales avoid carelessness, and act as a constant restraining influence upon the weakness of human nature. Nevertheless excellent results can be obtained by approximated diets, especially when the diabetic state is not severe. Models or the use of a standard cup, a ruler, and a set of standard spoons, fulfill the equipment requirements. Approximated diets tend to promote guessing, and their success depends upon the mental honesty of the patient. Free diets are not approved. The low fat high carbohydrate diet tolerates considerable variation in carbohydrate taken without appreciably affecting the blood sugar. Excess of fat leads immediately to a higher insulin requirement.

The diabetic tolerates more carbohydrate if he eats often. The utilization of carbohydrate improves as the day progresses. Accordingly small feedings of carbohydrate between meals and in the evening may be introduced when the carbohydrate intake reaches 100 grams. This may be given as 10 grams in the mid morning and mid afternoon and 20 grams before retiring. This leaves approximately 110 grams or more to be divided in fairly equal parts for the three main meals. However as the daily quantity of carbohydrate intake approaches or passes 200 grams the between meal feedings can be increased to 20, 20, and 20 grams. The morning and afternoon feedings should be in the form of fruit juices while in the evening the feedings should be a soda biscuit and a glass of milk as they are more slowly absorbed. Such a division of carbohydrate in the principal meals and the between meal feedings requires the least insulin.

All treatment should strive for complete control of the diabetic state. This implies (1) a diet sufficient in calories to maintain weight but not overweight, while in the obese under fifty a regime should be planned through diet and exercise to reduce the weight (2) a blood sugar not exceeding 150 mg per cent at any time in the twenty four hours, and (3) the absence of glycosuria.

### The Low Fat High Carbohydrate Diet

The system of building the patient up to the maintenance diet that has been found to be satisfactory follows:

DAY	PROTEIN GM	FAT GM	CARBOHYDRATE GM
1	50	50	50
2	60	50	70
3	70	50	90
4	70	50	110
5	70	50	130
6	70	50	150
7	70	50	170
8	70	50	190
9	70	50	210
10	70	50	230
11	70	50	250

This plan requires eleven days for completion. The protein is varied with the individual men doing physical work requiring 80 to 100 grams while many

TABLE V

## SAMPLE MENU FOR DAY (LOW FAT HIGH CARBOHYDRATE DIET)

	WEIGHT GM	PROTEIN GM	FAT GM	CARBOHY- DRATE GM
<i>Breakfast</i>				
Grapefruit juice	100	-	-	5
Oatmeal (cooked)	100	3	-	12
Milk	80	■	3	4
Egg	1	7	5	-
Bread (toasted)	20	2	-	10
Butter	2	-	2	-
Marmalade	10	-	-	9
		14	10	40
<i>Forenoon</i>				
Apple	90	-	-	10
<i>Dinner</i>				
Consommé	200	-	-	-
Liver	80	10	4	2
Butter	6	-	5	-
Potato	100	2	-	20
Carrots	100	1	-	9
Asparagus	100	1	-	2
Bread	50	5	1	26
Butter	5	-	4	-
Milk	40	1	2	2
Fresh peaches	200	-	-	19
		26	10	50
<i>Afternoon</i>				
Bread (toasted)	20	2	-	10
Butter	2	-	4	-
Jam	12	-	-	10
Tea with lemon	200	-	-	-
		2	4	20
<i>Supper</i>				
Tomato slices	100	1	-	3
Iceas	100	3	-	10
Celery	50	1	-	2
Lettuce	50	-	-	1
Cold sliced chicken	50	12	6	-
Bread	50	5	1	26
Milk	150	5	■	8
Butter	8	-	7	-
Banana	10	1	-	14
Orange	100	-	-	10
Sugar	6	-	-	6
		28	20	80
<i>Evening</i>				
Orange juice	200	-	-	20
Total values for day		70	50	250

NOTE All vegetables steamed : All foods canned in syrup washed in strainer before serving

TABLE VI (A)  
FOOD VALUES (COMMONER FOODS)

VEGETABLES FRESH				
ARTICLE	PROTEIN PER CENT	FAT PER CENT	CARBOHYDRATE PER CENT	CALORIES PER 100 GM
Lettuce	-	-	2	8
Cucumbers	-	-	2	8
Spinach	2	-	2	16
Asparagus	1	-	2	12
Rhubarb	-	-	2	8
Celery	1	-	3	16
Tomatoes	1	-	3	16
Brussels sprouts	1	-	3	16
Watercress	1	-	3	16
Cauliflower	2	-	4	25
Cabbage	2	-	-	29
Radiates	1	-	4	25
Pumpkin	1	-	6	29
String beans	2	-	6	33
Turnips	1	-	6	29
Squash	1	-	8	37
Beets	1	-	9	41
Carrots	1	-	9	41
Onions	1	-	9	41
Parsnips	1	-	11	49
Peas	7	-	15	90
Corn	3	-	19	90
Potato	2	-	20	90
Lima beans	7	-	22	119
Sweet potatoes	2	-	20	115
VEGETABLES CANNED				
Asparagus	1	-	2	10
Brussels sprouts	1	-	3	16
Tomatoes	1	-	3	16
String beans	1	-	3	16
Pumpkin	1	-	6	29
Peas	3	-	10	53
Corn	3	-	18	86
BERBIES AND FRUITS FRESH				
Strawberries	1	-	5	25
Grapefruit	-	-	5	21
Lemons	1	-	-	33
Watermelons	-	-	7	29
Blackberries	1	-	8	34
Cranberries	-	-	8	33
Peaches	-	-	9	37
Muskmelons	-	-	10	41
Raspberries	1	-	10	45
Oranges	-	-	10	41
Apples	-	-	11	45
Pears	-	-	11	45
Pineapples	-	-	12	49
Grapes	-	-	15	62
Cherries	-	-	17	70
Figs	1	-	17	74
Plums	1	-	17	74
Prunes	-	-	19	78
Bananas	1	-	20	86
Dates	2	-	54	234

TABLE VI (A)—CONT'D

ARTICLE	PROTEIN PER CENT	FAT PER CENT	CARBOHYDRATE PER CENT	CALORIES PER 100 GM
<b>BERRIES AND FRUITS CANNED</b>				
Peaches (water packed)	-	-	7	29
Pears (water packed)	-	-	9	37
Peaches	-	-	11	43
Blueberries	-	-	11	33
Pineapples	-	-	15	62
Oranges	-	-	18	74
<b>DAIRY PRODUCTS LIQ</b>				
Milk, whole	3	4	5	70
Milk, condensed	9	9	11	111
Milk, skimmed	3	-	5	33
Cream, 15 per cent fat	3	15	4	164
Cream, 20 per cent fat	-	18	4	192
Cream, 40 per cent fat	1	40	1	388
Buttermilk	3	-	5	34
Butter	-	85	-	491
Olive oil	-	100	-	930
Egg yolk	7	5	-	72
Egg white	11	-	-	45
Egg yolk	15	31	-	368
<b>CHEESE</b>				
American pile	23	36	-	453
Cottage cheese	17	2	1	186
Swiss	25	34	-	419
Brie	5	38	-	374
<b>MEATS</b>				
Beef, cooked				
Roast	22	28	-	351
Round steak fat removed	27	8	-	185
Chopped beef fat removed	20	8	-	150
Beef, canned				
Dried beef	39	5	-	206
Mutton, cooked				
Leg roast	25	22	-	301
Pork				
Ham smoked lean	20	20	-	268
Bacon smoked	10	55	-	646
Bacon crisp lean	10	-	-	41
Veal, cooked				
Leg roast	21	4	-	123
Chicken, cooked				
Roast	22	10	-	183
Boiled	17	11	-	172
Turkey cooked (roast)	27	18	-	278
Squab one (approximate)	12	5	-	96
Liver (uncooked)	20	5	2	131
<b>FISH FRESH</b>				
Cod	16	-	-	66
Cod salt	27	-	-	111
Flounder	14	-	-	57
Haddock	17	-	-	70
Halibut	18	5	-	120
Mackerel	18	7	-	159
Salmon	22	13	-	211
Shad	18	9	-	158
Trout, brook	19	11	-	97
Trout lake	17	10	-	163
Blue fish	19	1	-	87
Finnan haddock	22	-	-	90
White fish	23	6	-	150

TABLE VI (A)—CONT'D

ARTICLE	PROTEIN PER CENT	FAT PER CENT	CARBOHYDRATE PER CENT	CALORIES PER 100 GM
SHELLFISH				
Clams	8	1	~	50
Lobster	16	1	~	75
Oysters	6	1	3	46
Scallops	13	~	3	74
FLOUR MEALS BREAD CEREALS				
Bread white	9	1	52	250
Bread graham	9	~	52	269
Wheat flour	8	1	76	324
Cornmeal	8	5	74	383
Oatmeal dry	16	7	67	405
Oatmeal (cooked weight)	3	~	12	62
Cornflakes	7	~	79	353
Rice	8	~	79	357
Rice boiled	3	~	24	111
Macaroni	13	1	74	366
Macaroni cooked	3	1	16	87
BEVERAGES				
Ginger ale	~	~	8	33
Carbonated drinks (bottled soda sarsaparilla birch beer root beer)	~	~	8	33

TABLE VI (B)

FOOD ARRANGED ACCORDING TO CARBOHYDRATE CONTENT

(For Use With Approximated Diet)

VEGETABLES (FRESH OR CANNED)

5 Per Cent		10 Per Cent	15 Per Cent	20 Per Cent
1 to 3 per cent	3 to 5 per cent			
Lettuce	Tomatoes	String beans	Green peas	Potatoes
Cucumbers	Cauliflower	Brussels sprouts	Parsnips	Shell beans
Spinach	Egg plant	Pumpkin	Lima beans (very young)	Baked beans
Asparagus	Cabbage	Turnips	Green corn (very young)	Lima beans
Rhubarb	Radishes	Squash		Green corn
Celery	String beans (very young)	Beets		Boiled rice
Mushrooms	Summer squash	Carrots		Boiled macaroni
		Onions		
		Green peas (very young)		

FRUIT (FRESH OR CANNED)

5 Per Cent	10 Per Cent	15 Per Cent	20 Per Cent
Fresh	Fresh	Fresh	Fresh
Grapefruit	Leaches	Apples	Cherries (sweet)
Strawberries	Pineapple	Pears	Figs
Watermelon	Oranges	Grapes	Plums
Canned	Lemons	Blueberries	Bananas
Peaches (water packed)	Cranberries		
Blackberries (water packed)	Muskmelons		
	Raspberries		
	Apricots		
	Blackberries		
	Gooseberries		
	Currants		
	Cherries (sour)		

women receive 70 to 80 gms. In the case of inactive women 200 gms of carbohydrate will usually maintain weight. High strung males not infrequently require 275 grams of carbohydrate. Carbohydrate values of 300 grams have been used in cases complicated by pulmonary tuberculosis, lung abscess, or other infections. As the carbohydrate reaches 150 grams the insulin requirement frequently rises, but as the higher values are given mild hypoglycemic reactions develop. The nitrogen equilibrium upon the maintenance diet is satisfactory and due to the low fatty acid:glucose ratio there is no danger of acidosis.

In order to safeguard the growing child from vitamins A and D deficiency a cod liver oil concentrate rich in these vitamins should be given. The low calcium content should also be corrected by taking one quart of whole or skimmed milk daily.

### The Treatment of Complications

**Acidosis (Ketosis).**—The treatment of diabetic ketosis is an emergency. The two most important points are the relief of dehydration and the acceleration of carbohydrate oxidation by insulin.

The initial insulin dose should be 50 to 100 units of crystalline zinc insulin (regular or unmodified) according to the age of the patient, the severity of the acidosis, the presence or not of infection, and the previous insulin requirement. In very urgent cases part of the initial dose may be given intravenously. Subsequently at two hourly intervals three to four doses of twenty units should be given. From then on for the next six hours 10 units of insulin will be needed every two hours. The milder cases of acidosis will require about 100 units of insulin during the first twelve hours while the severe ones may need up to 300 units during the same interval. Diabetic acidosis or coma can be treated satisfactorily by a large single dose of protamine zinc insulin supplemented by crystalline zinc insulin. This procedure reduces the necessity of so many doses of crystalline insulin; this is most successful and safer in the hands of those more experienced in treating diabetic coma. Two hours after the first insulin 10 gms of glucose or its equivalent should be given every one to two hours until the ketosis has been relieved. An intake of 50 to 100 gms of carbohydrate during the first twelve hours is desirable. This intake of glucose does no harm, avoids the danger of hypoglycemia, and results in greater carbohydrate oxidation. Each urine specimen voided should be examined for sugar and diacetic acid. If possible urine should be obtained at two hour intervals but catheterization is not justified. The qualitative reaction for sugar in the urine is the best guide for insulin dosage: 20 units for a red test, 15 for a yellow, and 10 for a yellow green test as advocated by Joslin.

From the onset it is necessary to relieve dehydration. An initial intravenous administration of 1000 cc. of physiological saline or an equal amount of 1/6 molar sodium lactate is indicated. This may be repeated if necessary. As soon as possible start fluid by mouth 50 cc. every fifteen minutes for five hours. An intake of at least 2000 cc. of fluid is essential during the first twenty four hours. If vomiting or marked nausea is present a thorough

Gastric lavage with warm water should be given until the washings are clear. Before withdrawal of the tube 100 cc. of physiological saline should be left in the stomach. If vomiting continues the lavage should be repeated. After any gastric lavage no food or fluid should be given by mouth for two hours. The rate of output of urine is a fair guide to the amount to be given. If there is a pronounced anuresis the intake should be curtailed. There may be a coincident and excessive loss of potassium (see page 875) leading to muscular paralysis.

The only indication for circulatory stimulants is in those cases showing a falling blood pressure with hemoconcentration. They should be handled in the same manner as a case of shock due to water and electrolyte loss although plasma may be used. This complication may occur when there has been considerable delay in initiating treatment.

Allalies should be used only when there has been loss of base as shown by a delay in the return of the plasma  $\text{CO}_2$  capacity to normal. This base loss may result from a prolonged acidosis and is especially liable to occur if a renal complication has interfered with the ability of the kidney to manufacture ammonia. The excretion of the ketone bodies as ammonium salts conserves large amounts of sodium to the body fluids. In chronic nephritis part of the acidosis may be of a retention nature and is helped by base. Then the ketonuria will disappear before the plasma  $\text{CO}_2$  capacity reaches normal. If allalies are employed it must never be given intravenously but only by mouth. Doses of 4 grains of  $\text{NaHCO}_3$  every three hours for two to four doses in cool water will supply the base required but this may be even better supplied by disodium hydrogen phosphite as its secretion as dihydro sodium phosphite removes an hydrogen ion and liberates sodium to make up the deficit.

There is little justification today for the death of a case of uncomplicated diabetic coma. If complicated by pneumonia or acute nephritis the prognosis is grave. Failure of kidney function renders the outcome serious. Delay in the initiation of treatment is a common cause of failure. A patient unconscious for six to twelve hours before treatment is started may recover chemically but die from circulatory failure. When treating coma in the home or in the country in order to avoid the danger of hypoglycemia and to make use of large amounts of insulin permit a moderate glycosuria until the ketonuria has disappeared.

**Gangrene**—The basis of gangrene is an impaired circulation. This is mainly due to arteriosclerosis. Superadded is the hyperglycemia of the uncontrolled diabetic state. Something can be accomplished in preventing gangrene and this prophylactic treatment rests upon three points: (1) control of the diabetic state; (2) cleanliness of the feet; and (3) avoidance of minor injury to the feet. It is unusual to see gangrene develop with good diabetic control even if there is a marked degree of circulatory impairment. Failure to keep the feet clean renders them susceptible to infections from minor abrasions. Take great care in cutting corns and toe nails. For detailed directions as to the care of the feet refer to Joslin's *Treatment of Diabetes* page 691 5th edition.

Gangrene most commonly involves one or more toes. It may be dry or infected (moist). With it there may be an associated osteomyelitis. The treatment requires complete bed rest with slight elevation of the affected limb. A dry dressing should be applied, and all pressure of the bedclothes taken off the foot by the use of a footboard. These measures are only for protection. If it should never be applied, in fact, it is better to keep the part cool. In under these circumstances less blood is required for the nutrition of the part. The diabetic state should be strictly controlled with a diet containing at least 150 grams of carbohydrate and the necessary insulin. An estimation should be made of the efficiency of the circulation, but there are no criteria that will predict with accuracy the capacity to heal. The case that fails to localize the gangrenous area after strict diabetic control has been established will require amputation. If the gangrene is moist and spreading, the urgency of an amputation is much greater due to the danger of infection.

For many years the diabetic clinic in the Royal Victoria Hospital has adopted a conservative attitude in the treatment of gangrene in the diabetic. From 1925 to 1934, there were 118 cases of gangrene of the lower extremity. Of these 118 cases, 31 per cent were healed by medical means alone, 18 per cent had conservative operative procedures, usually the amputation of one or more toes, and 47 per cent suffered amputation at the knee or through the lower thigh. There was one lower leg amputation. A 47 per cent incidence of major amputations in such a series of gangrene is very low. Since the introduction of the low fat high carbohydrate diet the necessity for major amputation has dropped to 39 per cent. This policy has been pursued with slight modification. Minor repetitive amputations of the toes or trans tarsal operations have been become more frequent for economic reasons. The length of time consumed by the conservative medical measures sometimes offered a serious obstacle to the continuation of the treatment. Therefore these operations and even amputations below the knee at the site of election have increased in number.

As the state of the circulation is of such great importance measures to bring about permanent improvement are often given serious consideration. These are lumbar sympathectomy and uterine denervation. Their indications rest upon the proof that vasodilatation can be produced even when all the evidences of impairment of the circulation, particularly with skin and soft tissue atrophy are present.

The use of passive vascular exercises according to the principle of Hermann and Reid or Landis has been of great aid in a few cases of limited dry gangrene. It is contraindicated in infections. The gradual alteration of pressure (Hermann and Reid) is probably to be preferred when stimuli treatment, but later the sudden change of pressure (Landis) gives better results. Lately definitely better results have been obtained by intermittent venous occlusion as reported by Collens and Wilensky. Following periods of venous congestion there occurs a definite state of hyperemia as reported by Lewis and Grant in 1925. This hyperemic phase, under optimal conditions may result in a 600 per cent increase of blood flow. To it the main therapeutic benefit of this



method of treatment may be ascribed. With a blood pressure cuff about the mid thigh, pressures ranging from 40 mm of Hg to the diastolic level have been used, maintained for two minutes and released for two minutes and so on from two to six hours a day. The lower pressures are probably indicated in the presence of infection. In the author's hands this procedure in a limited number of cases of gangrene of the lower extremities in diabetics has given outstanding results. An automatic apparatus for carrying out this therapy is now available (Collins intermittent venous occlusion apparatus). As an index of the development of collateral circulation weekly measurements of the rise of the skin temperature of the foot after immersion of the arms in hot water is valuable. Since the treatment of gangrene in a diabetic is a tedious affair special provision should be made for exercise by a frame over the bed. As infections both tend to lead to gangrene and are serious complications antibiotics should be used as a prophylactic. The most usual organism is the *Staphylococcus aureus*. Therefore penicillin or streptomycin are particularly indicated (see Chapter XX).

In few departments of medicine is a closer cooperation between physician and surgeon required than in the handling of gangrene in the diabetic. Consideration of age, prolonged hospitalization, subsequent usefulness, and financial status have to be dealt with. The danger of recurrence of gangrene is not appreciable provided diabetic control is maintained and the proper care of the feet taken.

**Infections**—An infection in a diabetic requires prompt treatment. This is especially true if the diabetic state is uncontrolled. If the infection occurs in an extremity where there is impaired circulation the urgency is all the greater. Treatment consists in the strict control of the diabetic state. To accomplish rapid reduction of hyperglycemia give insulin every three hours and collect urines at the same intervals. The insulin dosage should vary as the severity of the diabetes and the degree of infection. Twenty or 30 units per dose are usually sufficient. When the Benedict reaction becomes yellow halve the insulin dose. Extremely severe infections require massive amounts of insulin. A patient with an extensive purulent infection of a thigh received 500 units of insulin in five hours without any lowering of the blood sugar. Following drainage of retained pus less insulin will be required. The rapidity of spread of an infection is remarkably influenced by the diabetic control. Lymphangitis may subside and cellulitis become localized.

Free incision is sometimes indicated but not nearly as often as before the advent of sulfonamides and antibiotic. This is particularly so with furuncles and carbuncles. But before they are employed a culture of the infected area should be made to determine the infecting organism and its susceptibility to one or more of these specific agents. The character of the organism will often give a direct lead but this should be confirmed. In many cases the organism can be deduced fairly accurately by the character of the lesion. In carbuncles it is usually the *Staphylococcus aureus*. In deeper cases of cellulitis it may be the *Streptococcus hemolyticus* or some other less frequent invader while in pneumonia it is usually the pneumococcus but may be one of the other two or *H. influenzae*, *H. tuberculosis* or a virus infection. If therapy is started be

fore a culture is taken, one is always in a state of doubt as to whether the best therapeutic agent is being used. At times the urgency of the condition does not warrant delay in therapy before a definite result of the culture is obtained while in others a bacteriological service is not available. Under these conditions full doses of sulfadiazine, penicillin, streptomycin or other antibiotic is indicated. It is shotgun therapy and may turn the trick. When the type of organism and its sensitivity are definitely known, more specific therapy can be employed.

Before this era carbuncles were extensively incised, with a resulting large cavity for granulation and slow healing. At present this is not done. There may be multiple punctures of the area with silver nitrate to relieve tension or even aspiration of the necrotic fluid, with injection of the specific therapeutic agent in equivalent amounts so as not to produce tension in the tissues or a single small incision may be made for drainage.

These same general rules may be applied whatever the infection may be. But there are certain rules in connection with infections of the toes and feet, in particular which must be emphasized. These are:

1 Never apply a moist dressing if there is hyperglycemia or impaired circulation. Use dry dressings only.

2 Never apply or bathe the feet in strong antiseptic solutions (iodine, lysol, etc.)

3 Control the hyperglycemia before extensive incision or drainage.

4 If hyperglycemia has been controlled and there is good palpable pulsation in the dorsalis pedis vessel, interrupted moist dressings without rubber protective can be safely used.

**Hyperthyroidism**—Hyperglycemia and glycosuria occur frequently in cases of toxic goiter. The degree of glycosuria is mild, and the fasting blood sugar is normal. This hyperglycemia is dependent upon faulty or impaired glycogen formation and storage by the liver and disappears after the hyperthyroidism has been controlled. One must not confuse this type of glycosuria with the true diabetic state associated with toxic goiter. Both conditions must be recognized and treated. Neither of these conditions is rare and the chances of their occurring in the same individual are not remote. The real danger is the acceptance of the glycosuria as being a simple manifestation of the hyperthyroidism and not due to a truly diabetic state. Coma never occurs in hyperthyroidism except in the extreme stages of a thyrotoxic crisis and is then due to circulatory failure or/and hyperpyrexia. Indications of acidosis such as acetoneuria are not present unless due to starvation while the CO<sub>2</sub> combining power of the plasma is within normal limits. In fact there may be hyperpnea in order to satisfy the excessive oxidation requirements and the CO<sub>2</sub> combining power may be elevated.

This combination is well demonstrated by a middle aged woman in a state of unconsciousness from a diabetic ketosis with a high blood sugar and glycosuria. Her pulse rate was 160 per minute, the skin was warm and moist and there was slight fullness with increased vascularity of the thyroid gland. To suit able treatment for the acidosis 90 minims of Lugol's solution per day were given. In twenty four hours her pulse dropped by crisis to 90 per minute, the acidosis had been relieved, and one week later a bilateral thyroidectomy was

done without the pulse rate rising above 100 per minute. Today after an interval her basal metabolic rate is normal and the diabetic state is under good control by diet and 40 units of insulin.

### The Use of Insulin

Insulin is an aid, not a cure, in the treatment of diabetes. Its use is indicated when a diet suitable for the needs of the patient will not alone control the diabetic state. Insulin is practically inactive by mouth, so has to be given subcutaneously. In emergencies it may be used intravenously.

There are three main types of insulin being used in North America today, namely crystalline zinc (regular unmodified) protamine zinc and globin. Commercially these insulins are prepared in 40 and 80 units per c.c. strengths. It is good practice to use a strength that will avoid a volume of fluid larger than 1 c.c. These insulins have different periods of action. Crystalline zinc has its peak action in 1 to 4 hours with a total 12 hours' action. Protamine zinc has a 24 to 28 hour action and at no one time is there any large amount of free insulin liberated from the mixture. Globin insulin has an intermediate position its duration of action being from 16 to 20 hours. Crystalline zinc and globin insulin should be given 30 minutes before meals so as to bring about the hypoglycemic effect of the meal. Protamine zinc insulin is usually given before breakfast but there is no advantage in waiting 30 minutes after its administration before eating.

In the course of treating every diabetic a decision has to be made—does or does not the patient need insulin? If he does the next decision is the type of insulin to be used. For the new untreated adult diabetic a satisfactory scheme to follow is to start the patient on a small dose (12 to 16 units) of protamine zinc insulin before breakfast. Build up this dose progressively by 4 unit increments as you are increasing the diet until the fasting urine is free from glycosuria. Then check the fasting blood sugar which should be normal. With one dose of protamine zinc insulin a day taken before breakfast the fasting blood sugar is the lowest in the 24 hours and the highest blood sugar is usually found one hour after the noon meal. After the fasting blood sugar is normal investigate the urine and blood sugar one hour after the noon meal. If there is no glycosuria and the blood sugar does not exceed 150 mg. per cent you have good control of your diabetic with one dose of protamine zinc insulin. This is only possible in the milder group of diabetics that need insulin.

When the diabetic state is more severe the blood sugar one hour after the noon meal will be well above 150 mg. per cent and then it is necessary to supplement the protamine zinc with crystalline zinc insulin. The latter dose initially a small one (8 to 12 units) should be given 30 minutes before breakfast followed by the protamine zinc dose. The crystalline zinc dose is increased by increments of 4 units until the blood sugar 4 hours after its administration is normal. Then study the level of the blood sugar one hour after the noon meal. If it does not exceed 150 mg. per cent you have good control with one dose of protamine zinc and one dose of crystalline zinc insulin both before breakfast. If the blood sugar one hour after the noon meal is still high it will be necessary to start a crystalline zinc dose 30 minutes before

fore a culture is taken, one is always in a state of doubt as to whether the best therapeutic agent is being used. At times the urgency of the condition does not warrant delay in therapy before a definite result of the culture is obtained, while in others a bacteriological service is not available. Under these conditions full doses of sulfadiazine, penicillin, streptomycin, or other antibiotic is indicated. It is shotgun therapy and may turn the trick. When the type of organism and its sensitivity are definitely known more specific therapy can be employed.

Before this era carbuncles were extensively incised with a resulting large cavity for granulation and slow healing. At present this is not done. There may be multiple punctures of the necr. with silver nitrate to relieve tension or even aspiration of the necrotic fluid with injection of the specific therapeutic agent in equivalent amounts so as not to produce tension in the tissues or a single small incision may be made for drainage.

These same general rules may be applied whatever the infection may be. But there are certain rules in connection with infections of the toes and feet, in particular which must be emphasized. These are:

1 Never apply a moist dressing if there is hyperglycemia or impaired circulation. Use dry dressings only.

2 Never apply or bathe the feet in strong antiseptic solutions (iodine, lysol, etc.).

3 Control the hyperglycemia before extensive incision or drainage.

4 If hyperglycemia has been controlled and there is good palpable pulsation in the dorsalis pedis vessel, interrupted moist dressings without rubber protective can be safely used.

**Hyperthyroidism**—Hyperglycemia and glycosuria occur frequently in cases of toxic goiter. The degree of glycosuria is mild and the fasting blood sugar is normal. This hyperglycemia is dependent upon faulty or impaired glycogen formation and storage by the liver and disappears after the hyperthyroidism has been controlled. One must not confuse this type of glycosuria with the true diabetic state associated with toxic goiter. Both conditions must be recognized and treated. Neither of these conditions is rare and the chances of their occurring in the same individual are not remote. The real danger is the acceptance of the glycosuria as being a simple manifestation of the hyperthyroidism and not due to a truly diabetic state. Coma never occurs in hyperthyroidism except in the extreme stages of a thyrotoxic crisis and is then due to circulatory failure or/and hyperpyrexia. Indications of acidosis such as acetoneuria are not present unless due to starvation while the  $\text{CO}_2$  combining power of the plasma is within normal limits. In fact there may be hyperpnea in order to satisfy the excessive oxidation requirements and the  $\text{CO}_2$  combining power may be elevated.

This combination is well demonstrated by a middle-aged woman in a state of unconsciousness from a diabetic ketosis with a high blood sugar and glycosuria. Her pulse rate was 160 per minute, the skin was warm and moist, and there was slight fullness with increased vascularity of the thyroid gland. To suit able treatment for the acidosis 90 minims of Lugol's solution per day were given. In twenty-four hours her pulse dropped by crisis to 90 per minute, the acidosis had been relieved and one week later a bilateral thyroidectomy was

done without the pulse rate rising above 100 per minute. Today, after many years, her basal metabolic rate is normal and the diabetic state is under good control by diet and 40 units of insulin.

### The Use of Insulin

Insulin is an aid, not a cure, in the treatment of diabetes. Its use is indicated when a diet suitable for the needs of the patient will not alone control the diabetic state. Insulin is practically inactive by mouth, so has to be given subcutaneously. In emergencies it may be used intravenously.

There are three main types of insulin commonly used in North America today, namely crystalline zinc (regular unmodified), protamine zinc and globin. Commercially these insulins are prepared in 40 and 80 units per c.c. strengths. It is good practice to use a strength that will avoid a volume of fluid larger than 1 c.c. These insulins have different periods of action. Crystalline zinc has its peak action in 3 to 4 hours with a total 12 hours action. Protamine zinc has a 24 to 28 hour action and at no one time is there any large amount of free insulin liberated from the mixture. Globin insulin has an intermediate position, its duration of action being from 16 to 20 hours. Crystalline zinc and globin insulin should be given 30 minutes before meals so as to balance the hyperglycemic effect of the meal. Protamine zinc insulin is usually given before breakfast but there is no advantage in waiting 30 minutes after its administration before eating.

In the course of treating every diabetic a decision has to be made—does or does not the patient need insulin? If he does, the next decision is the type of insulin to be used. For the new untreated adult diabetic a satisfactory scheme to follow is to start the patient on a small dose (12 to 16 units) of protamine zinc insulin before breakfast. Build up this dose progressively by 4 unit increments as you are increasing the diet until the fasting urine is free from glycosuria. Then check the fasting blood sugar which should be normal. With one dose of protamine zinc insulin a day taken before breakfast the fasting blood sugar is the lowest in the 24 hours and the highest blood sugar is usually found one hour after the noon meal. After the fasting blood sugar is normal investigate the urine and blood sugar one hour after the noon meal. If there is no glycosuria and the blood sugar does not exceed 150 mg. per cent you have good control of your diabetic with one dose of protamine zinc insulin. This is only possible in the milder group of diabetics that need insulin.

When the diabetic state is more severe the blood sugar one hour after the noon meal will be well above 150 mg. per cent and then it is necessary to supplement the protamine zinc with crystalline zinc insulin. The latter dose initially a small one (8 to 12 units) should be given 30 minutes before breakfast followed by the protamine zinc dose. The crystalline zinc dose is increased by increments of 4 units until the blood sugar 4 hours after its administration is normal. Then study the level of the blood sugar one hour after the noon meal. If it does not exceed 150 mg. per cent you have good control with one dose of protamine zinc and one dose of crystalline zinc insulin both before breakfast. If the blood sugar one hour after the noon meal is still high it will be necessary to start a crystalline zinc dose 30 minutes before

fore a culture is taken one is always in a state of doubt as to whether the best therapeutic agent is being used. At times the urgency of the condition does not warrant delay in therapy before a definite result of the culture is obtained while in others a bacteriological service is not available. Under these conditions full doses of sulfadiazine, penicillin, streptomycin or other antibiotic is indicated. It is shotgun therapy and may turn the trick. When the type of organism and its sensitivity are definitely known, more specific therapy can be employed.

Before this era carbuncles were extensively incised with a resulting large cavity for granulation and slow healing. At present this is not done. There may be multiple punctures of the ulcer with silver nitrate to relieve tension or even aspiration of the necrotic fluid, with injection of the specific therapeutic agent in equivalent amounts so as not to produce tension in the tissues or a single small incision may be made for drainage.

These same general rules may be applied whatever the infection may be. But there are certain rules in connection with infections of the toes and feet in particular which must be emphasized. These are:

1 Never apply a moist dressing if there is hyperglycemia or impaired circulation. Use dry dressings only.

2 Never apply or bathe the feet in strong antiseptic solutions (iodine, lysol, etc.).

3 Control the hyperglycemia before extensive incision or drainage.

4 If hyperglycemia has been controlled and there is good palpable pulsation in the dorsalis pedis vessel, interrupted moist dressings without rubber protective can be safely used.

**Hyperthyroidism.**—Hyperglycemia and glycosuria occur frequently in cases of toxic goiter. The degree of glycosuria is mild and the fasting blood sugar is normal. This hyperglycemia is dependent upon faulty or impaired glycogen formation and storage by the liver and disappears after the hyperthyroidism has been controlled. One must not confuse this type of glycosuria with the true diabetic state associated with toxic goiter. Both conditions must be recognized and treated. Neither of these conditions is rare and the chances of their occurring in the same individual are not remote. The real danger is the acceptance of the glycosuria as being a simple manifestation of the hyperthyroidism and not due to a truly diabetic state. Coma never occurs in hyperthyroidism except in the extreme stages of a thyrotoxic crisis and is then due to circulatory failure or/and hyperpyrexia. Indications of acidosis such as acetoneuria are not present unless due to starvation while the CO combining power of the plasma is within normal limits. In fact there may be hyperpnea in order to satisfy the excessive oxidation requirements and the CO combining power may be elevated.

This combination is well demonstrated by a middle aged woman in a state of unconsciousness from a diabetic ketosis with a high blood sugar and glycosuria. Her pulse rate was 160 per minute the skin was warm and moist and there was slight fullness with increased vascularity of the thyroid gland. To suit able treatment for the acidosis 90 minims of Lugol's solution per day were given. In twenty four hours her pulse dropped by crisis to 90 per minute the acidosis had been relieved and one week later a bilateral thyroidectomy was

hours after its administration although some patients may develop hypoglycemia in the late afternoon from a before breakfast crystalline zinc dose. Globin insulin given before breakfast will usually have its low point in the late afternoon although hypoglycemia may occur in the forenoon.

An insulin reaction not explained by some irregularity in insulin dosage or food eaten, may be due to (1) an unusual amount of exercise, (2) delayed absorption of food or (3) an improvement of carbohydrate tolerance (greater output of endogenous insulin). The effect of exercise upon insulin requirement is so striking that Joslin considers that it stands next to diet and insulin in the treatment of diabetes. Delayed digestion and absorption of food occurs in patients whose general vitality is low. These reactions may be severe and dangerous.

Patients should be taught to be suspicious of any uncomfortable sensations occurring at the times when insulin reactions might occur. By paying attention to mild symptoms and treating them serious symptoms will be avoided. The patient who disregards mild symptoms, on subsequent days will develop severe ones. All patients starting insulin should be intentionally given a mild reaction so that they will recognize it in the future and experience the result of treatment. This is of special importance because recurring hypoglycemia in the same patient tends to develop similar symptoms.

Mild and moderate hypoglycemia from crystalline zinc and globin insulin is satisfactorily treated by 5 grams of glucose or its equivalent every ten minutes by mouth until all symptoms are abolished. If unconsciousness has developed 10 grams of glucose intravenously will wake up the patient to be followed by 5 grams by mouth as necessary. Glucose by rectum in a larger dose (15 grams) is effective. Glucose prepared in 5 gram powders is convenient but orange juice, corn syrup or glucose candies will do as well. To meet an emergency 1 cc of 1 in 1000 solution of adrenalin chloride may be given to an adult. This will cause a temporary rise in the blood sugar provided there is glycogen in the liver. Adrenalin when used must always be followed by glucose otherwise the patient will revert into a more severe hypoglycemic state. To a child one half of the above dose of adrenalin may be given. Following an insulin reaction the diet should remain unchanged but the insulin must be decreased. Hypoglycemia from protamine zinc insulin should first be treated with 5 gm of glucose or its equivalent and in 10 minutes 100 cc of milk (1 glass) and a soda biscuit. Protamine zinc reactions tend to recur thus the necessity for giving a more slowly absorbing form of carbohydrate. In an adult the insulin responsible should be reduced by 4 units in a child by 2 units. All insulin reactions should be systematically treated and indiscriminate eating discouraged. Every patient taking insulin should always carry with him the means of treating a reaction as well as an identification card stating that he has diabetes is taking insulin and the dose being taken. Such a precaution may be life saving.

If insulin is injected too frequently into the same area the subcutaneous tissues become nodular from delayed absorption. Accordingly the arms and

the noon meal. Thus the milder cases that need insulin will be controlled by one dose of protamine zinc while the severer cases may require a dose of protamine zinc before breakfast and a dose of crystalline zinc before breakfast before dinner, and even before the night meal.

When crystalline zinc insulin is used alone a single dose before breakfast is rarely satisfactory. It is usually necessary to give a dose before breakfast and 1/2 gm before supper. These doses should be equal in unitage if possible. In the severer cases a noon dose will be necessary, this to be smaller than the morning and night doses. Most diabetics can be nicely controlled by day with crystalline zinc insulin but in the severer cases the blood sugar rises after midnight to reach its highest level before breakfast.

Since globin insulin is an intermediate insulin it can be used to handle the day period in many cases while protamine zinc is employed to cover the night hours. Globin insulin given before breakfast can often be substituted for 2 doses of crystalline zinc insulin with good results. In the milder cases one dose of globin insulin alone before breakfast may carry the patient through to a satisfactory blood sugar before breakfast the next morning.

The efficiency of insulin is in part dependent upon the management of the diet. It is our plan to introduce between meal feedings when the total carbohydrate of the diet reaches 150 grams. These consist of 10 grams of carbohydrate in the forenoon, 10 grams in the afternoon and 15 grams in the evening. After the total between meal values have been subtracted from the total values of the day the balance is divided equally between the three main meals. The between meal feedings may be varied considerably to meet the individual case. When using globin insulin better control is established with a smaller breakfast so the main meals are one fifth, two fifths and two fifths of the remaining values.

**Complications.**—The main complication following insulin administration is hypoglycemia. This is due to great lowering of the blood sugar. In adults mild symptoms nervousness, tremor and palpitation appear when the blood sugar falls to 50 to 60 mg per cent. As the value drops to 40 to 50 mg per cent, sweating is constant and is the forerunner of the more serious signs. Convulsions, coma and death occur only with extremely low blood sugar values, 20 mg per cent or less. Children can have much lower blood sugar values without symptoms than adults. Values of 30 mg per cent are not unusual. The rate of drop of the blood sugar especially in elderly arterio-sclerotic patients influences the level at which symptoms appear. With a rapidly dropping blood sugar in such cases the author has seen moderate symptoms at 100 mg per cent. Children also complain of double vision adults may simulate alcoholic hilarity while rarely patients may become unconscious without warning. Headache as a symptom of hypoglycemia from protamine zinc insulin is not uncommon. Rarely is it seen with crystalline zinc insulin.

Insulin reactions must be coordinated with the kind of insulin that is being used. Protamine zinc reactions occur after midnight usually from 3 to 7 AM. The earlier in the night that it occurs the greater is the disproportion between dosage and requirement. Crystalline zinc reactions occur 3 to 4



hours after its administration although some patients may develop hypoglycemia in the late afternoon from a before breakfast crystalline zinc dose (lobin insulin given before breakfast will usually have its low point in the late afternoon although hypoglycemia may occur in the forenoon).

An insulin reaction not explained by some irregularity in insulin dosage or food eaten may be due to (1) an unusual amount of exercise (2) delayed absorption of food or (3) an improvement of carbohydrate tolerance (greater output of endogenous insulin). The effect of exercise upon insulin requirement is so striking that Joslin considers that it stands next to diet and insulin in the treatment of diabetes. Delayed digestion and absorption of food occurs in patients whose general vitality is low. These reactions may be severe and dangerous.

Patients should be taught to be suspicious of any uncomfortable sensations occurring at the times when insulin reactions might occur. By paying attention to mild symptoms and treating them serious symptoms will be avoided. The patient who disregards mild symptoms on subsequent days will develop severe ones. All patients starting insulin should be intentionally given a mild reaction so that they will recognize it in the future and experience the result of treatment. This is of special importance because recurring hypoglycemia in the same patient tends to develop similar symptoms.

Mild and moderate hypoglycemia from crystalline zinc and globin insulin is satisfactorily treated by a gram of glucose or its equivalent every ten minutes by mouth until all symptoms are abolished. If unconsciousness has developed 10 grams of glucose intravenously will "wake up" the patient to be followed by 5 grams by mouth as necessary. Glucose by rectum in a 10% dose (10 grams) is effective. Glucose prepared in a 5% powder is convenient but orange juice, corn syrup or glucose candies will do as well. To meet an emergency 1 cc of 1 in 1000 solution of adrenalin chloride may be given to an adult. This will cause a temporary rise in the blood sugar provided there is glycogen in the liver. Adrenalin when used must always be followed by glucose otherwise the patient will revert into a more severe hypoglycemic state. To a child one half of the above dose of adrenalin may be given. Following an insulin reaction the diet should remain unchanged but the insulin must be decreased. If hypoglycemia from protamine zinc insulin should first be treated with a 10 cc of glucose or its equivalent and in 10 minutes 100 cc of milk (1 glass) and a soda biscuit. Protamine zinc reactions tend to recur thus the necessity for giving a more slowly absorbing form of carbohydrate. In an adult the insulin responsible should be reduced by 4 units in a child by 2 units. All insulin reactions should be systematically treated and indiscriminate eating discouraged. Every patient taking insulin should always carry with him the means of treating a reaction as well as an identification card stating that he has diabetes is taking insulin and the dose being taken. Such a precaution may be life saving.

If insulin is injected too frequently into the same area the subcutaneous tissues become nodular from delayed absorption. Accordingly the arms and

the noon meal. Thus, the milder cases that need insulin will be controlled by one dose of protamine zinc while the severer cases may require a dose of protamine zinc before breakfast and a dose of crystalline zinc before breakfast before dinner and even before the night meal.

When crystalline zinc insulin is used alone a single dose before breakfast is rarely satisfactory. It is usually necessary to give a dose before breakfast and again before supper. These doses should be equal in unitage if possible. In the severer cases a noon dose will be necessary, this to be smaller than the morning and night doses. Most diabetics can be nicely controlled by day with crystalline zinc insulin but in the severer cases the blood sugar rises after midnight to reach its highest level before breakfast.

Since globin insulin is an intermediate insulin it can be used to handle the day period in many cases while protamine zinc is employed to cover the night hours. Globin insulin given before breakfast can often be substituted for 2 doses of crystalline zinc insulin with good results. In the milder cases one dose of globin insulin alone before breakfast may carry the patient through to a satisfactory blood sugar before breakfast the next morning.

The efficiency of insulin is in part dependent upon the management of the diet. It is our plan to introduce between meal feedings when the total carbohydrate of the diet reaches 150 grams. These consist of 10 grams of carbohydrate in the forenoon, 10 grams in the afternoon, and 15 grams in the evening. After the total between meal values have been subtracted from the total values of the day, the balance is divided equally between the three main meals. The between meal feedings may be varied considerably to meet the individual case. When using globin insulin better control is established with a smaller breakfast so the main meals are one fifth, two fifths, and two fifths of the remaining values.

**Complications.**—The main complication following insulin administration is hypoglycemia. This is due to great lowering of the blood sugar. In adults mild symptoms, nervousness, tremor, and palpitation appear when the blood sugar falls to 50 to 60 mg per cent. As the value drops to 40 to 50 mg per cent, sweating is constant and is the forerunner of the more serious signs. Convulsions, coma, and death occur only with extremely low blood sugar values, 20 mg per cent or less. Children can have much lower blood sugar values without symptoms than adults. Values of 30 mg per cent are not unusual. The rate of drop of the blood sugar especially in elderly arteriosclerotic patients influences the level at which symptoms appear. With a rapidly dropping blood sugar in such cases the author has seen moderate symptoms at 100 mg per cent. Children also complain of double vision, adults may simulate alcoholic hilarity while rarely patients may become unconscious without warning. Headache is a symptom of hypoglycemia from protamine zinc insulin is not uncommon. Rarely is it seen with crystalline zinc insulin.

Insulin reactions must be coordinated with the kind of insulin that is being used. Protamine zinc reactions occur after midnight usually from 3 to 7 a.m. The earlier in the night that it occurs the greater is the disproportion between dosage and requirement. Crystalline zinc reactions occur 3 to 4

hours after its administration although some patients may develop hypoglycemia in the late afternoon from a before breakfast crystalline zinc dose. Globin insulin given before breakfast will usually have its low point in the late afternoon although hypoglycemia may occur in the forenoon.

An insulin reaction, not explained by some irregularity in insulin dosage or food eaten, may be due to (1) an unusual amount of exercise, (2) delayed absorption of food or (3) an improvement of carbohydrate tolerance (greater output of endogenous insulin). The effect of exercise upon insulin requirement is so striking that Joslin considers that it stands next to diet and insulin in the treatment of diabetes. Delayed digestion and absorption of food occurs in patients whose general vitality is low. These reactions may be severe and dangerous.

Patients should be taught to be suspicious of any uncomfortable sensations occurring at the times when insulin reactions might occur. By paying attention to mild symptoms and treating them serious symptoms will be avoided. The patient who disregards mild symptoms on subsequent days will develop severe ones. All patients starting insulin should be intentionally given a mild reaction so that they will recognize it in the future and experience the result of treatment. This is of special importance because recurring hypoglycemia in the same patient tends to develop similar symptoms.

Mild and moderate hypoglycemia from crystalline zinc and globin insulin is satisfactorily treated by 5 grams of glucose or its equivalent every ten minutes by mouth until all symptoms are abolished. If unconsciousness has developed 10 grams of glucose intravenously will wake up the patient to be followed by 5 grams by mouth as necessary. Glucose by rectum in a larger dosage (15 grams) is effective. Glucose prepared in 5 gram powders is convenient but orange juice, corn syrup or glucose candies will do as well. To meet an emergency 1 cc of 1 in 1000 solution of adrenalin chloride may be given to an adult. This will cause a temporary rise in the blood sugar provided there is glycogen in the liver. Adrenalin when used must always be followed by glucose otherwise the patient will revert into a more severe hypoglycemic state. For a child one half of the above dose of adrenalin may be given. Following an insulin reaction the diet should remain unchanged but the insulin must be decreased. Hypoglycemia from protamine zinc insulin should first be treated with 50 cc of glucose or its equivalent and in 10 minutes 100 cc of milk (1% fat) and a soda biscuit. Protamine zinc reactions tend to recur thus the necessity for giving a more slowly absorbing form of carbohydrate. In an adult the insulin responsible should be reduced by 4 units in a child by 2 units. All insulin reactions should be systematically treated and indiscriminate eating discouraged. Every patient taking insulin should always carry with him the means of treating a reaction as well as an identification card stating that he has diabetes is taking insulin and the dose being taken. Such a precaution may be life saving.

If insulin is injected too frequently into the same area the subcutaneous tissues become nodular from delayed absorption. Accordingly the arms and

legs should be used in rotation, avoiding any thickened areas. Rarely at the site of repeated insulin injections a complete atrophy of the subcutaneous fat takes place leaving a groove. When such happens the area should be avoided as a site of further injections. Daily massage will gradually restore the normal contour of the part.

In the early days of insulin a great deal of trouble was experienced with allergic reactions. They varied from a local erythema with induration at the site of injection to a systemic urticaria with extreme facial edema. The protein content of the fluid was usually the cause, but cases of sensitivity to the preservative used, or the reaction of the fluid have been seen. Today individuals sensitive to insulin are observed infrequently. If the sensitization is mild all evidence of it usually disappears after a few weeks. Changing to a more concentrated solution is sometimes effective. Pork or sheep insulin should be tried when beef insulin is not tolerated. The use of the antihistamine drugs is helpful.

About 30 per cent of patients who start insulin have been able to discontinue it within two years. This should dispel the idea widespread among the laity that once insulin always insulin.

### The Use of Drugs

Exclusive of insulin there are no drugs that have any curative effect in the treatment of diabetes. Many preparations, patented or otherwise, are advertised as being effective by mouth but they are useless. Other drugs should be used to alleviate symptoms as in nondiabetics.

### Exercise and Carbohydrate Tolerance

Before insulin the value of exercise in lowering the blood sugar of a mild diabetic was well appreciated. Since exogenous insulin can supply the endogenous deficiency, exercise is applicable to all diabetics today provided their general condition does not contraindicate it. The blood sugar lowering from exercise is most marked in the child and necessitates extra carbohydrate before strenuous games and gym classes. Even during hospital periods less insulin is required if regular exercise can be arranged for. The bedridden diabetic with gangrene of the lower extremity should have daily exercise of the arms. So great is the improvement from exercise that a precautionary lowering of the insulin dosage upon discharge from the hospital is advisable.

### The Diabetic Child

The diabetic child is a growing organism and therefore requires special care. The diet should be readjusted at yearly intervals. Height and weight should be followed and overweight must be rigorously avoided. During the period of puberty special care is necessary.

The nutrition of the diabetic child should be based upon actual height. Diets for diabetic children should be calculated upon theoretical weight for actual height. Since some of these children are considerably overweight for their age a compromise in the values of the diet has to be made.

A dietetic plan for children from birth to 20 years of age that has been found to be fairly satisfactory is as follows:

AGE PERIOD	TOTAL CALORIES PER KILO	PROTEIN GM PER KILO	FAT GM	CHOC GM
0 to 5 years	100 to 80	3	50 to 60	20 to 30
6 to 10 years	80 to 60	4	60 to 70	20 to 30
11 to 15 years	60 to 40	5	70 to 80	20 to 30
16 to 20 years	40 to 30	6	80 to 90	20 to 30

The above scheme provides the maintenance values. The child should be built up to these values by graded stages from a lower diet. When actual height is normal for age the scheme requires very little modification. Children should have three main meals with forenoon, afternoon and evening feedings. After subtraction of the between-meal feedings from the total values the remaining values should be divided equally between the three meals. All diabetic children's diets should be calculated and weighed in the metric system.

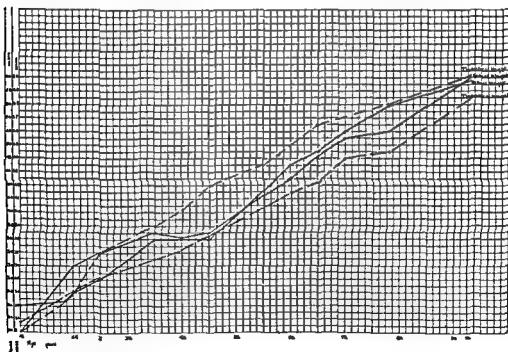


Chart XXVII—Height and weight curves of a diabetic child treated with insulin as compared with the average normal. Onset of diabetes at eighteen months.

In addition to the calories care should be taken to supply a normal amount of calcium (milk). Vitamin supplements are essential.

During the first year of diabetic life in a child there may be very little tendency for the blood sugar to rise in the night so crystalline zinc insulin two doses a day can be used and good control maintained. This is helpful for the mother in that insulin reactions then occur by day and are more easily handled. Shortly however fasting hyperglycemia will appear in most cases,

and the use of protamine zinc and crystalline zinc insulin are imperative. Some cases are being well controlled by combinations of protamine zinc and globin insulin.

The future of these children depends upon their control. The incidence of complications is much higher in the poorly controlled cases.

Diabetic children respond readily to exercise by a lowering of the blood sugar. "Gym" classes should be preceded by five or ten grams of extra carbohydrate. Contact with open cases of tuberculosis should be strictly avoided.

### Diabetes and Pregnancy

In the preinsulin era the incidence of fertility of diabetic women was low, varying from 2 to 6 per cent in different clinics. The cause of this low fertility was not exactly known, but most probably it was related to the degree of undernutrition as well as the partial failure of pituitary function (gonadotrophic factor) resulting in infantile development of the uterus and amenorrhea.

With the insulin era the pregnancy rate has increased to about 50 per cent. Also large numbers of diabetic children have now reached maturity and have borne children. The pregnancy risk for the mother in a diabetic patient is not much greater than in a nondiabetic woman. White has reported a maternal survival rate of 99.6 per cent in a series of 271 consecutive diabetic pregnancies. This figure is even better than the accepted 96 per cent for nondiabetic women. Such a satisfactory survival rate has not been attained for the fetus and until recent years the advent of insulin did not greatly lower the fetal mortality. More recently, with careful correction of the imbalance of sex hormones, White has been able to raise the fetal survival rate to 90 per cent. This is a triumph for modern medicine.

The main abnormalities that contribute to the high fetal mortality are vascular disease, hypoovarism and uterine intractability in the mother. Imbalance of the sex hormones and water retention leading to hydramnios and fetal edema are also of major importance. Lumbly oversized infants and atelectasis contribute to the picture. Of all the above abnormalities the imbalance of the sex hormones is the most important.

An imbalance of the sex hormones is present in about 50 per cent of diabetic pregnancies and manifests itself by a low pregnandiol excretion, a low serum level of estrin and a high serum level of chorionic gonadotrophin.

The dietetic management of the mother does not need to be changed with the onset of pregnancy. The low fat high carbohydrate diet has been found satisfactory. The protein intake should be at least  $1\frac{1}{2}$  to 1½ grams per kilo gram of body weight. Extra calcium and vitamin intake is essential. The regular insulin requirement does not change appreciably until the start of the third trimester when it tends to increase. A successful outcome depends a great deal upon the strict control of the diabetic state. Those cases that show hormonal imbalance is determined by high serum prolactin (chorionic gonadotrophin), and low pregnandiol excretion and if they show associated signs of toxemia such as increasing blood pressure, albuminuria and edema, had best be treated, according to White, with progesterone and estrogen.

In the main the best type of delivery is by cesarean section. Only those cases that are mild have borne children previously and have shown no sign of toxicity should be allowed to deliver themselves. Primiparous mothers, those who have lost a previous pregnancy and those who have experienced toxemia or hormonal imbalance should be delivered by cesarean section toward the end of the thirty seventh week.

After delivery the mother is best handled with crystalline zinc insulin for a few days. If there has been an increasing insulin requirement prior to delivery it will be necessary to reduce the dosage rather rapidly to the patient's basic level.

The blood sugar of the infant is usually normal at birth but tends to be unstable and may fall during the first four hours to mild hypoglycemic levels. Feedings of 5 grams of glucose in water every two hours from birth for 48 hours will prevent hypoglycemia.

### Surgical Operations Upon Diabetics

Excluding surgical interference for complications referable to the diabetic state (infections and gangrene with arteriosclerosis of the lower extremity) there is no surgical operation today that cannot be carried out upon the controlled diabetic with practically the same risk that is incurred with the nondiabetic, the physical state in other respects being equal. In fact our diabetics after major operations (cholecystectomies, appendectomies, thyroidectomies, etc.) suffer less postoperative vomiting and discomfort than a comparable group of nondiabetics. This is due to a greater attention to detail and more care as to the maintenance of a proper glycogen reserve both preoperatively and postoperatively. The tissues of the controlled diabetic heal at a normal rate provided there is no impairment of circulation.

The preoperative preparation of the diabetic should assure an adequate glycogen reserve, freedom from acidosis and dehydration and a blood sugar below 150 mg per cent. If time is available the carbohydrate intake should be from 150 to 200 grams per day for two days preoperatively. Sufficient insulin should be given to assure utilization. On the day of the operation and for a few days postoperatively we prefer to use crystalline zinc insulin because of the shorter duration of action in a period of uncertain food intake. On the morning of the operation breakfast is omitted and a small dose of crystalline zinc insulin is given. Postoperatively an intravenous injection of 1000 cc of 5 per cent glucose and saline along with 16 to 20 units of crystalline zinc insulin is given. This may be repeated 6 hours later using 5 per cent glucose in water. Subsequently for one to two days 10 to 15 grams of carbohydrate at two to three hour intervals are given and covered with insulin. With the taking of soft food four light meals containing the total values of protein 50 grams, fat 50 grams and carbohydrate 100 grams are tried. Insulin is given before the first, second and fourth meals. As recovery progresses these values are increased in protein and carbohydrate and a three meal regime is established.

With the aid of insulin the kind of anesthetic is of less importance than formerly. Chloroform and protracted ether administration should be strictly

avoided Nitrous oxide and oxygen, ethylene, spinal, or local anesthesia, are to be preferred. Ether, if used, should be removed from the tissues by rebreathing or by breathing 5 per cent  $\text{CO}_2$  in oxygen. This avoids nausea, vomiting, and inability to take fluids.

### The Instruction of the Diabetic

The success of all diabetic treatment depends upon an intelligent cooperation on the part of the patient. To gain such cooperation it is imperative that certain rudimentary knowledge of the disease and its care be given. This is best accomplished by organized classes of instruction as found in diabetic clinics.

The diabetic should know as a minimum

- 1 A brief story of the nature of his disease and the importance of diet in its treatment, the commoner complications and how they can be avoided (coma, gangrene, infections)

- 2 The preparation of the diet, weighed or approximated. If weighed, the calculation of the diet in the metric system.

- 3 The administration of insulin, the recognition of hypoglycemia and its treatment.

- 4 Examination of the urine for sugar (Benedict's or Clinistest) and for diacetic acid (ferric chloride).

- 5 What to do as to diet and insulin if glycosuria or hypoglycemia appear.

- 6 Care of the feet (especially applicable to patients over fifty years of age).

During the period of instruction Joslin's *Diabetic Manual* is a valuable source of information for the patient. From the onset a notebook should be kept which in time will be helpful for reference.

### The New Disease

With the prolongation of life referable to insulin, the medical profession is today confronted with a new disease. What is the complete future of the diabetic child is still unknown. Those of us who have seen these children grow to maturity, marry, bear children of their own, and take their part in the modern world, realize keenly the tremendous progress in the treatment of diabetes mellitus.

### HYPERINSULINISM

Hyperinsulinism is the syndrome of spontaneous intermittent or continuous loss of consciousness with or without convulsions, from excessive production of insulin by the pancreatic islands of Langerhans. The usual symptoms of hypoglycemia occur, namely, nervousness, tremor, perspiration, and palpitation, progressing as the blood sugar falls and finally convulsions, loss of consciousness and even death.

This condition has been recognized only in recent years as the understanding of the insulin reaction has become more general. The pancreatic



lesion usually found has been either an hypertrophy of the island tissues, an adenoma, or a carcinomatous growth. Rarely has the lesion been extrapancreatic as in Anderson's fatal case due to an adrenal tumor. Many instances are on record where no specific lesion could be found at operation or autopsy to account for the spontaneous hypoglycemia. Surgical removal of a pancreatic tumor has effected a cure in a limited number of cases.\*

**Symptoms**—The symptoms of hyperinsulinism are dependent upon the degree of lowering of the blood sugar and its duration. Most adults start to develop nervousness, tremor and palpitation with a blood sugar of 60 mg per cent, while children may not show any symptoms until the value has reached 30 mg per cent. Due to their late onset in children, the symptoms progress more rapidly, loss of consciousness with convulsions occurring with little warning.

**Diagnosis**—An exact diagnosis depends upon coordinating the attacks with a blood sugar low enough to account for them. To do this, those cases having intermittent attacks will have to be kept under supervision. Fasting or strenuous physical exercise may be helpful to initiate an attack in doubtful cases. The therapeutic effect of 5 or 10 grams of glucose administered either by mouth or intravenously is also of great aid. Marked improvement should be prompt but temporary. The use of the glucose time curve is of diagnostic value. It should be carried on for six hours. A hypoglycemic blood sugar level after the third hour is significant.

The following criteria are generally considered essential for the diagnosis of organic hyperinsulinism:

1. Fasting blood sugars below 60 mg per cent
2. Immediate relief of proved hypoglycemia with intravenous glucose
3. A characteristic glucose tolerance test
4. A capacity above the normal to remove glucose from the blood stream when glucose is administered intravenously at a constant rate

Hyperinsulinism is most frequently mistaken for epilepsy or hysteria but the character of the attack coordinated with the clinical picture and the blood sugar should make differentiation easy.

**Treatment**—Medical treatment in severe cases is unsatisfactory. The necessity for almost continuous carbohydrate administration makes it impracticable. But in moderate cases, particularly those in which no anatomical explanation is found, small and evenly distributed carbohydrate meals are helpful. Some patients maintain a better blood sugar on high protein and high fat meals rather than upon high carbohydrate feedings. High carbohydrate meals tend to be followed by marked hypoglycemia. Epinephrin (0.5 to 1 cc) helps to overcome acute attacks while nembutal and amytal have a beneficial effect. Surgical exploration in clear cut cases is justified and recommended. Removal of an adenoma has resulted in a cure. Partial removal of an abnormal pancreas has led to some improvement †

\*The senior author has seen four cases which immediately followed so called attacks of influenza but eventually developed signs of Parkinson's disease.

†In one case which required further observation for many months ergoklonin (Wyeth) gave decided relief of symptoms and prevented the pronounced fall of blood sugar after a carbohydrate meal.

## RENAL GLYCOSURIA

### (Renal Diabetes)

Renal glycosuria is a condition where sugar (glucose) is passed in the urine at the time when the blood sugar is normal. This is due to a lowered glucose threshold in the kidney. The condition *per se* results in no symptoms, there is no impairment of health, and there is no justification for dietetic restriction. Accordingly in true cases there is no interference with the normal expectation of life.

There are three main types of renal glycosuria, (1) hereditary or idiopathic, (2) cyclic, and (3) when associated with pregnancy. The *idiopathic type* is a clear cut entity, unchanging when observed over many years. These individuals have a lowered glucose threshold in the kidneys so that they constantly excrete small amounts of dextrose. Many individuals of the same family may be affected, and the condition persists for life. The *cyclic type* is a recurring mild glycosuria in digestive periods when the blood sugar is below the normal threshold. There is no glycosuria in the fasting state due to the threshold being only slightly lowered. This diagnosis in the past has been made largely through the study of venous blood, which offers a chance for error. A synchronous determination of the arterial or capillary blood sugar after immersion of the arm in hot water has shown that when this cyclic glycosuria occurs the arterial sugar value is frequently above the normal threshold level of 170 mg. per cent. Thus many of these cases are really mild diabetics. *Renal glycosuria associated with pregnancy* is not uncommon. In pregnancy there is a temporary lowering of the renal threshold for glucose so that the findings may be identical with the hereditary type. After delivery the threshold returns to its normal level, the glycosuria ceasing only to recur with subsequent pregnancies.

**Pathogenesis**—With Richard's studies upon the kidney function, the mechanism of the glucose threshold in the kidney has been explained. The glomerular fluid would appear to be a true filtrate through Bowman's capsule. Its concentration in glucose is the same as that of the blood in the afferent artery coming to the glomerulus. As the glomerular fluid passes downward through the convoluted tubules glucose is rapidly absorbed. Thus glucose absorption is a specific function of the cells lining the proximal convoluted tubules. These cells may fail to reabsorb the glucose completely, with the result that a small amount remains in the tubular fluid and reaches the pelvis of the kidney in the urine. To date no histological alteration has been noted in the tubular cells of idiopathic cases of renal glycosuria. However, renal glycosuria is frequently observed in diseases where there is tubular cell degeneration (see Fig. 321).

**Diagnosis**—The exact diagnosis of renal glycosuria necessitates a careful coordination of the blood and urine sugar levels in synchronous periods. Care must be taken to consider the glucose threshold in the kidney in terms of arterial blood or its equivalent. Only in the fasting state are the venous and arterial values identical. In all digestive periods the arterial sugar is

somewhat higher than the venous due to removal of glucose from the capillary blood. The attempt to judge renal glucose thresholds from the venous blood in the digestive state invalidates a large amount of the published data.

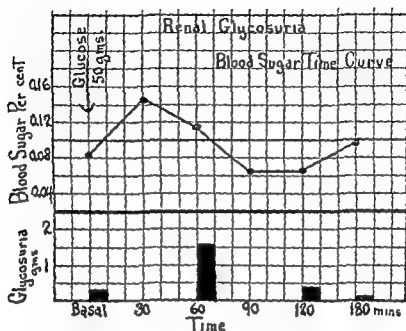


Chart XXVIII — Blood sugar curve in a case of renal glycosuria

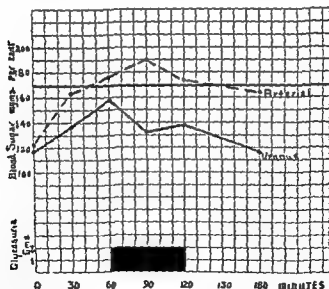


Chart XXIX — A threshold determination in renal glycosuria obtained by comparing venous and capillary blood sugar curves. Note parallelism of the level of the capillary blood sugar and glycosuria.

True renal glycosuria is present almost continuously and the threshold can frequently be determined by examination of the urine and venous blood hourly in the fasting state. The level of the blood sugar at which the

glycosuria ceases is the threshold. This may be 100 mg. per cent or even lower. The writer has seen cases with thresholds of 70 mg. per cent, so low that glycosuria continued even when the fasting state was prolonged from 8 A.M. to 2 P.M. The twenty-four hour glucose excretion usually does not exceed 10 grams, and is only slightly influenced by the carbohydrate intake. The blood sugar (venous) curve after the administration of 100 grams of glucose by mouth should be normal with the maximum value in thirty minutes, and not exceeding 150 mg. per cent. The return to the fasting level should follow in one and a half to two hours, following which there should be a temporary period of mild hypoglycemia. Frequently the glucose time curve indicates a tolerance greater than the average normal. In the case of the renal glycosuria of pregnancy the glucose time curve may show delayed glycogen storage, probably due to a deficiency of liver glycogen through increased demand.

Uncomplicated cases of renal glycosuria have no symptomatology, and observation over several years shows no change in the threshold or glycosuria. No progression into diabetes mellitus has been observed. In the diagnosis of all nondiabetic glycosurias the exact chemical nature of the reducing substance present should be determined. In renal glycosuria it is always dextrose.

A more complete study of these cases would include evidence obtained by respiratory studies, that the oxidation rate of carbohydrate by the tissues was normal.

One must remember that renal glycosuria and diabetes mellitus can occur in the same case. Only after the hyperglycemia has been controlled does the persistent slight glycosuria point to a lowered renal threshold. Renal glycosuria is frequently seen in cases of degenerative tubular nephritis (nephrosis) where it may persist until death. It has also been observed in temporary degenerative lesions of the kidney.

**Treatment**—The typical case of renal glycosuria needs no special treatment. Dietetic restriction is definitely contraindicated, and when employed through misdiagnosis frequently results in marked loss of weight. However at yearly intervals for several years the patient should be reexamined both as a protection to himself and to the doctor.

The cyclic type of renal glycosuria should be watched more carefully and checks carried out upon the arterial or capillary bloods at three month intervals. Many of these cases will be found to be mild diabetics.

Since the renal glycosuria of pregnancy is only temporary and presents all the features of the true renal glycosuria no special treatment is necessary.

### ACID BASE BALANCE

The animal organism will not tolerate changes of its internal environment and exerts great adaptability in circumventing them and maintaining an exquisite equilibrium. The one most jealously guarded is the hydrogen ion concentration which is maintained by the acid base balance. It is true that the constitution of the blood is not constant in all its parts nor is it an absolute index at all times of the hydrogen ion concentration of the cells. To some

extent it can be used as an index or a reflection of the cellular condition in this regard. The venous blood contains more carbon dioxide and lactic acid than does the arterial blood. This would suggest that the former would be more acid than the latter but when it is appreciated that oxyhemoglobin is more acid than the reduced hemoglobin it will be obvious that there is a fairly steady balance indicated by the venous blood. The principal means for maintaining the constancy of the hydrogen ion equilibrium at short notice is by the cellular dissociation of carbon dioxide thus changing the ratio of  $\frac{H^+ CO_3}{B H CO_3}$ . It has been stated that the blood may act as an indicator of the condition in the cells. This is hardly true but rather it reflects the tendency of the hydrogen ion concentration of the internal environment to be modified in one or other direction. It is often stated that the pH of the blood has either risen or fallen a certain degree. It is, therefore, inferred that the pH of the cells has likewise changed. It is doubtful whether any of our modern physical instruments are delicate and accurate enough to register the changes in pH which a cell could tolerate. It has been difficult to determine the range over which the hydrogen ion concentration of a mammalian cell can be modified and still maintain its functional activity.

There is a small group of cells in the midbrain called the respiratory center, which has a functional rather than a strictly anatomical entity. It has been postulated that this center is so sensitive to changes in pH that it responds to changes which cannot be detected by our best physical methods. I do not think that it is taking too much for granted if we presume that all cells are equally sensitive to changes in their hydrogen ion concentration, but the cells of the respiratory center are more articulate in this regard. The  $\frac{H^+ CO_3}{B H CO_3}$  ratio can be looked upon as the fine adjustment in the maintenance of this imperative equilibrium. If for any reason the hydrogen ion concentration of the tissues in general tends to increase to the minutest degree the respiratory center responds by increasing the pulmonary ventilation. This reduces the  $CO_2$  in the alveolar air, which in turn increases its diffusion outward and lowers its concentration in the arterial blood which affects the ratio in the cells and so the equilibrium is maintained. On the contrary if the hydrogen ion concentration declines the stimulation to the respiratory center is depressed and pulmonary ventilation is reduced thus allowing  $CO_2$  of the alveolar air to rise and in turn affect the ratio in an opposite direction by the retention of carbon dioxide.

Carbon dioxide on account of its great solubility, its weak acid character and its easy dissociation is an ideal substance for the maintenance of this delicate equilibrium. Through the vicissitudes of the ordinary daily life of an average normal individual changes in the alveolar air and blood can be detected as for instance during the cycle of digestion when there is a large outpouring of acid ions in the gastric juice the  $CO_2$  combining power of the blood and its percentage in the alveolar air rises but a short time later when the relatively all alyne pancreatic and biliary excretions take place the

opposite occurs. This can also be repeated by the ingestion of relatively large amounts of alkaline or acid substances.

The range over which carbon dioxide elimination or retention can exert its influence on the constancy of the cellular pH is a comparatively narrow one, and if the body were solely dependent upon it, we should be in a constant state of hyperpnea or apnea. The lungs may be looked upon as the fine adjustment while the coarse regulation is to be found in the renal function. The normal urine is acid in reaction. The ingestion of a sufficient amount of base to influence the pH of the blood promptly brings about a diuresis, and an excessive alkaline secretion which may be sufficient to render the urine alkaline. On the contrary, if acid substances are ingested, the urine becomes more acid. The response of pulmonary ventilation to such changes is instantaneous, while the renal response shows a certain inertia. All of these variations of blood pH, pulmonary and renal function can be quite easily demonstrated in the normal man. A simpler experiment can be undertaken by voluntarily modifying the degree of pulmonary ventilation. Prolonged hyperpnea with atmospheric air will be followed by a period of apnea the length of which will be determined by the interval which must elapse before the pH of the respiratory center has returned to normal. There has been produced a condition commonly known as an uncompensated gaseous alkalosis. On the contrary, if the inspired air is enriched with carbon dioxide (5 to 10 per cent), increasing pulmonary ventilation may not be able to maintain the alveolar  $\text{CO}_2$  at its normal level. Therefore there will be a progressive accumulation of  $\text{CO}_2$  in the blood and the tissues. The excretion of base by the kidneys is rapidly reduced but in the interval there is an uncompensated gaseous acidosis. This latter condition is not usually met with in clinical medicine, but the former—uncompensated gaseous alkalosis—often results from hysterical or other neurotic forms of hyperpnea, and may be so pronounced as to produce an alkalosis sufficiently intense to cause tetany.

The common terms which are used to indicate these variations in the acid base balance are acidosis and alkalosis. They refer however, to changes in the blood rather than to any demonstrable change in cells, although they strongly indicate that such a trend is in operation. It would seem best to outline the signs and symptoms of these two conditions and follow with an account of their occurrence in pathological conditions.

### ACIDOSIS

The first sign of acidosis is an increase in the pulmonary ventilation. This takes place through augmentation of the individual respirations. In a mild acidosis this may be detected only by the experienced observer, but as it progresses, it is obvious to the least initiated that there is an increased respiratory effort. It is commonly known as "air hunger" or "Kussmaul's respiration." The carbon dioxide percentage in the alveolar air is reduced, as is also the  $\text{CO}_2$  combining power of the plasma. The urine is highly acid and if the renal function is unimpaired will contain large amounts of chlorides, phosphates, and sulfates in combination with base. Ammonia acting in this capacity will be increased to save the loss of base and the phosphates will

appear as acid sodium phosphates. There is also a diuresis and a progressive anhydremia. The other signs are headache, anorexia, nausea, vomiting abdominal cramps, pains in the limbs, weakness, lassitude and coma, with death if the acidosis is severe and prolonged. Cyanosis is not present despite the shift of the oxyhemoglobin curve to the right as the hyperpnea maintains a high partial pressure of oxygen in the alveolar air. If such a state is maintained more than a few hours irreparable cellular damage occurs, and although the acidosis may be corrected the effects produced are not reversible and death occurs.

The causes of acidosis are

- (a) Loss of base
- (b) Diminished absorption of base
- (c) Increased formation of acid
- (d) Decreased elimination of acid

The primary loss of base or all  $\text{HCl}$  is a comparatively rare clinical condition but may be due to a loss of pancreatic juice through a fistula, persistent vomiting particularly when there is a low gastric acidity and regurgitation of alkaline intestinal contents into the stomach in bichloride of mercury poisoning due to a loss of base in the stools and in children with severe diarrhea. Even rarer is the diminished absorption of base. It is sometimes encountered in chronic intestinal lesions which lead to diminished absorption but the clinical alkalosis is usually overshadowed by a hypocalcemia probably due to the same cause.

An increased formation of acid is the commonest cause of acidosis. The simplest example is excessive muscular exertion when there is an oxygen debt and an accumulation of lactic acid in the blood. It will be mentioned below how there is in methyl alcohol poisoning, a severe acidosis through the formation of formic acid. Diabetes mellitus presents a well known cause of acidosis through the formation and accumulation of acetoacetic and  $\beta$  oxybutyric acids derived from incomplete oxidation of fats. They are commonly known as ketone bodies and their presence in the blood is called ketosis, and in the urine ketonuria. It must not be taken for granted, however that all instances of ketonuria are due to a primary acidosis. In severe alkalosis ketonuria may also be present. Acidosis of the same character as that of diabetes mellitus may result from a high fat diet or ketogenic starvation particularly in children. There are a number of other types of presumed acidosis but whether these are a true bill or not is questionable. Ether anesthesia is usually accompanied by signs of a mild acidosis but the exact method of its production if this be actually the case is open to debate. There is good evidence to suggest that it might be due to an increase in lactic acid or other unidentified acids, a migration of chlorides to the blood or to an excessive retention of carbon dioxide. This has not been proved and a decrease in pH precedes the fall in  $\text{CO}_2$ . It has been claimed that there is a decrease of the alveolar  $\text{CO}_2$  and a lowering of the alkali reserve in normal pregnancy but some workers have demonstrated that although the bicarbonate reserve decreases the pH increases, which would suggest that the changes in the blood of pregnancy might be an alkalosis. A somewhat similar

the form of sodium bicarbonate, or better as disodium phosphate, may be given but not to the exclusion of more fundamental procedures. The direct treatment of alkalosis is more urgent. This is best carried out by giving ammonium or calcium chloride by mouth, or weak hydrochloric acid intravenously. Calcium gluconate will often remedy the distressing and dangerous tetany. J. C. W.

## DIABETES INSIPIDUS

Diabetes insipidus is a syndrome usually due to a lesion of the base of the brain, and is characterized by an impelling thirst with a corresponding polyuria. The urine is of very low specific gravity and contains no sugar.

A great deal of confusion has persisted in the literature as to the fundamental nature of this syndrome, which can be better appreciated if viewed from an historical aspect. In 1674 Willis differentiated between diabetes mellitus and diabetes insipidus on the basis of sugar in the urine. In 1860 Claude Bernard produced a temporary polyuria with urine of low specific gravity by puncture of the floor of the fourth ventricle. Later Schaefer and his associates prepared an active principle from the posterior hypophysis and demonstrated its relationship to a diuresis. Larini, in 1913, went a step further and controlled the polyuria of diabetes insipidus by injections of the posterior lobe extract. Accordingly he postulated a state of hypofunction of the posterior hypophysis as the causal disturbance. In the same year, 1913, Camus and Roussy showed that hypophysectomy itself did not cause a polyuria unless there was an associated lesion of the floor of the third ventricle. Finally Richter in 1930, was able to produce a permanent polyuria in rats by puncture of the hypothalamus anterior to the tuber cinereum in the region of the chiasma. Thus a syndrome was produced, identical with that in diabetes insipidus, by a lesion of the anterior hypothalamus which at the same time was controlled by injections of the posterior hypophyseal extract. Today most clinicians consider the diabetes insipidus syndrome to arise from a lesion of the floor of the third ventricle of the brain anterior to the tuber cinereum. The lesion may be neoplastic, postinflammatory, luetic (tertiary lesion) or traumatic (postoperative). In a study of 107 cases recently reported 63 per cent showed a tumor of the base of the brain, 13 per cent had a syphilitic basis and 8 per cent had a nonspecific inflammatory lesion.

Diabetes insipidus may have an hereditary basis as well shown by the studies of Weil. Among 119 members of a family, 35 developed the syndrome. When hereditary, its onset is usually in infancy or early life, but these individuals may live to old age. The syndrome may be transmitted through both parents to both male and female children.

From the above it is evident that there are two groups of cases (1) 'primary' or 'idiopathic' where the cause is hereditary and (2) 'secondary' or 'symptomatic' where the syndrome results secondary to some organic lesion of the brain. The particular part of the brain usually involved is the area just anterior to the tuber cinereum in the floor of the third ventricle. The organic lesion is usually a tumor but may be of syphilitic origin, or post-inflammatory. Rarely the syndrome has followed a fracture of the base of



the skull a cerebral hemorrhage or a basilar meningitis. Those cases with an hereditary basis present simply the symptoms characteristic of diabetes insipidus. Where there is an associated brain lesion symptoms referable to it are also present.

**Symptoms**—The symptoms characteristic of the diabetes insipidus syndrome are polyuria and thirst. Polyuria is considered to be primary. There is a record of one case where it amounted to 43 liters in 24 hours (Trousseau). The thirst follows as a result of systemic dehydration. The onset may be gradual or acute. Rarely has a rapid onset been followed by as rapid a disappearance. The urine is pale of a low specific gravity (1.001 to 1.005), but the total solids are not reduced. Albumin and other abnormal constituents are not present. The kidney function is normal and there is no nonprotein nitrogen retention in the blood. Where water is withdrawn the dehydration may become extreme even resulting in convulsive seizures.

In the 'primary' or congenital type of the disease the syndrome may persist throughout life and the patient live to old age. When the symptoms have an organic brain lesion as their cause its nature will determine the outcome. Since the majority of these individuals have a brain tumor (usually a glioma), the duration of life is limited to months or a few years depending upon the rapidity of growth of the neoplasm. With the progress of the tumor emaciation and asthenia become marked.

**Pathological Anatomy**—The anatomical situation of the lesion in the 'symptomatic' group of diabetes insipidus would seem to be well established in the hypothalamic region. The antidiuretic effect of posterior pituitary extracts is also well established. Whether there is an anatomical and functional relationship between the two is still in doubt but nerve connections have been traced between the hypothalamic area and the posterior lobe of the pituitary via the infundibular stalk.

**Diagnosis**—The diagnosis is not difficult. The important point is the inability of the patient to concentrate the urine even with deprivation of water. The diagnostic use of a posterior pituitary extract hypodermically (1 c.c.) is of great help in doubtful cases. The temporary relief of the thirst with urinary concentration up to 1020 or above is characteristic. Hysterical polyuria is transitory. In chronic nephritis there is a polyuria of low specific gravity (1.006 to 1.010) but the clinical picture with hypertension, nitrogen retention and the presence of albumin and casts in the urine, should distinguish the two.

**Treatment**—The treatment of the syndrome should be directed toward control of the thirst and polyuria. This can be done with posterior pituitary extracts. Unfortunately their effect is transitory four to six hours so their administration has to be repeated. Hypodermic administration, by nasal spray or nasal jelly are equally effective. The dose must be determined for each individual usually 1 c.c. three to four times a day is necessary. A dose late in the evening allows undisturbed sleep. More recently pitressin in oil has been made available which has a 24 to 48 hour effect.

the form of sodium bicarbonate, or better as disodium phosphate, may be given but not to the exclusion of more fundamental procedures. The direct treatment of alkalosis is more urgent. This is best carried out by giving ammonium or calcium chloride by mouth, or weak hydrochloric acid intravenously. Calcium gluconate will often remedy the distressing and dangerous tetany. J. C. M.

## DIABETES INSIPIDUS

Diabetes insipidus is a syndrome usually due to a lesion of the base of the brain and is characterized by an impelling thirst with a corresponding polyuria. The urine is of very low specific gravity and contains no sugar.

A great deal of confusion has persisted in the literature as to the fundamental nature of this syndrome, which can be better appreciated if viewed from an historical aspect. In 1674 Willis differentiated between diabetes mellitus and diabetes insipidus on the basis of sugar in the urine. In 1860 Claude Bernard produced a temporary polyuria with urine of low specific gravity by puncture of the floor of the fourth ventricle. Later Schaefer and his associates prepared an active principle from the posterior hypophysis and demonstrated its relationship to a diuresis. Farini, in 1913, went a step further and controlled the polyuria of diabetes insipidus by injections of the posterior lobe extract. Accordingly he postulated a state of hypofunction of the posterior hypophysis as the causal disturbance. In the same year, 1913, Camus and Roussy showed that hypophysectomy itself did not cause a polyuria unless there was an associated lesion of the floor of the third ventricle. Finally Richter in 1930, was able to produce a permanent polyuria in rats by puncture of the hypothalamus anterior to the tuber cinereum in the region of the chiasma. Thus a syndrome was produced identical with that in diabetes insipidus by a lesion of the anterior hypothalamus, which at the same time was controlled by injections of the posterior hypophyseal extract. Today most clinicians consider the diabetes insipidus syndrome to arise from a lesion of the floor of the third ventricle of the brain anterior to the tuber cinereum. The lesion may be neoplastic, postinflammatory, luetic (tertiary lesion), or traumatic (postoperative). In a study of 107 cases recently reported 63 per cent showed a tumor of the base of the brain, 13 per cent had a syphilitic basis and 8 per cent had a nonspecific inflammatory lesion.

Diabetes insipidus may have an hereditary basis as well, shown by the studies of Weil. Among 119 members of a family, 35 developed the syndrome. When hereditary its onset is usually in infancy or early life but these individuals may live to old age. The syndrome may be transmitted through both parents to both male and female children.

From the above it is evident that there are two groups of cases: (1) 'primary' or 'idiopathic' where the cause is hereditary and (2) 'secondary' or 'symptomatic' where the syndrome results secondary to some organic lesion of the brain. The particular part of the brain usually involved is the area just anterior to the tuber cinereum in the floor of the third ventricle. The organic lesion is usually a tumor but may be of syphilitic origin, or postinflammatory. Rarely the syndrome has followed a fracture of the base of

Since the urine has a wide range of reaction there is a marked variation in the percentage of the total uric acid that may be free. At a pH of 5 three fourths of the total uric acid excreted is free while at a pH of 8 all of the uric acid is excreted as a salt. Normal urine has a pH around 6 at which reaction there are 2 parts of dissolved urates to one part of free uric acid. The main bases that participate in the excretion of uric acid as salts are ammonia, sodium and potassium.

**Uric Acid Metabolism in Gout**—In the blood of gouty subjects the uric acid is usually above the normal. This elevation is thought to be due to a defective renal excretion of uric acid (Folin). The power to destroy uric acid would not appear to be impaired since in gouty subjects less uric acid is excreted than in the normal individuals when it is ingested as purines.

Pratt has shown that between attacks the endogenous excretion of uric acid is less than in his normal controls. Just prior to an attack there is an appreciable drop in the urinary excretion during which period the blood value is rising. With the mitigation of the acute symptoms the urinary excretion increases and the blood reaches its highest concentration. At this point the deposition of the sodium monurate crystals takes place. This high concentration of urate in the blood is not the sole cause of the deposition, since there are other diseases such as leucemia and chronic nephritis in which higher blood values occur but deposition never takes place. There is some unknown factor which influences this.

**Etiology.—Heredity**—Continental and English studies would indicate a high transmission of the gouty diathesis through the male stock. Hospital patients in North America have not given such a history. When transmitted the abnormality usually remains latent until after thirty five years of age. Gout occurs rarely in childhood but when it does occur it is quite severe. (See 116, 126 and 327.)

**Alcohol**—Excess consumption of fermented liquors such as wines, beer, porter, and ale, have long been considered to have an etiological relationship to this disease. Nevertheless gout is seen in total abstainers. Whiskey gin and distilled spirits do not seem to have the same baneful influence.

**Excess Protein Consumption**—Overeating of large quantities of protein food especially meat is considered to break down a latent gouty diathesis. Such overeating is usually associated with obesity.

**Lead Poisoning**—Lead poisoning frequently leads to gout. This was recognized by Magnus Levy in 1899 who reported 36 cases of gout, 11 of which had definite lead poisoning. Multiple joints are frequently involved, and the disease runs a severe course.

**Symptoms.—Acute Gout**—The acute attack usually has a sudden onset although there may be prodromal symptoms of malaise and indigestion with flatulence. The onset is frequently at night with the metatarsophalangeal joint of one big toe the site of predilection. The pain like an "intense burning," causes great restlessness and the toe is extremely sensitive to jars vibration or touch. After a few hours as the pain abates the joint becomes reddened swollen with increased local heat. The veins are characteristically

More recent studies have shown that the antidiuretic factor is contained in the pressor fraction of this extract, but the therapeutic response when used in a refined form is not superior

There is no advantage in any reduction of fluid intake. A slightly restricted salt intake, 3 to 4 grams per day, is helpful

If the primary lesion is luetic, antisyphilitic treatment should be thoroughly carried out. Improvement in general health, and rarely almost complete relief of the symptoms may follow. Brain tumors of the hypothalamic region are usually inoperable

## GOUT

Gout for years has been considered to be an abnormality of uric acid metabolism. However we are not certain of the error in the intermediary purine metabolism but later work by Folin has supported the older contention by Garrod, that it is a matter of defective renal excretion of uric acid. At recurring intervals uric acid is retained in the blood partly free and partly as a sodium salt. When this concentration reaches a certain level an unknown factor initiates the deposition of sodium monourate crystals into and about the joints and tendons, which constitutes the acute attack of gout.

That gout may have further basic ramifications would be suggested from the studies of Talbot and his associates, who found that a diuresis appeared before any clinical or subjective evidence of gout was manifest. With this diuresis there was a negative sodium and chloride balance.

**Uric Acid Metabolism**—The nucleoproteins of our foods are hydrolyzed in the gastrointestinal tract into the purine substances which are absorbed into the blood stream as such. They are quite free from protein, phosphoric acid and sugar, which together with the purine make up the original nucleoprotein molecule. These purine bases are adenine and guanine which by a process of oxidation in the tissues are changed into uric acid through the stages of hypoxanthine and xanthine. Most probably this oxidation takes place in the liver as that organ is the only one from which an enzyme can be secured which is capable of changing xanthine into uric acid. As uric acid is an end product in human metabolism it has to be either destroyed or excreted. About 50 per cent of that formed in the body is excreted by the kidneys and the balance would appear to be destroyed most likely by the liver. That the body can destroy uric acid has not been proved but ingested purines or ingested uric acid can only be accounted for by excretion to the extent of about 50 per cent.

Man and the chimpanzee are different from other mammals in their inability to oxidize uric acid. The rest of the mammals oxidize uric acid into allantoin to as high as 80 to 98 per cent.

The concentration of uric acid in whole blood varies from 1 to 2 mg. per 100 cc. but in serum it is 3 to 4 mg. per 100 cc. By Folin's later method the normal range may be somewhat higher. Free uric acid crystals could never occur at the pH of the blood and other body fluids. In the extracellular fluids the main base is sodium thus sodium monourate is the salt formed.

prominent. There is moderate fever with a slight leucocytosis, and frequently an elevation of blood pressure. The duration of the attack is from one to several days, as a rule recurring at intervals of months or years.

*Chronic Gout*—Chronic gout differs from acute gout in that with recurring attacks tophi and bony changes develop that leave a permanently damaged joint. There may be a chronic stiffness or a mechanical interference with mobility. Frequently bursae become chronically thickened and may even contain crystals of sodium monourate. Such cases may have multiple joints involved, the hands, elbows, knees, ankles, etc.



Fig. 18.—X-ray of the foot in a case of chronic gout showing at the articulation of the tarsal and metatarsal bones near the articulation particularly the great toe and the little toe.

In addition to the arthritic signs of gout there is an irregular collection of conditions which are attributed to the so-called gouty diathesis. They are found in members of gouty families who do not necessarily have arthritis. The principal manifestations are eczema with fine silver white scales similar to psoriasis which indeed may be also present. There are frequently attacks of 'biliousness' or dyspepsia with a foul breath, furred tongue, constipation and an enlarged and tender liver. Migraine, myalgias, neuralgias, sciatica



Fig 3.6—A child suffring from a ricket. It is important to note the edema of the face, the atrophy of the limb, the tophi in the fingers and the knees which are conspicuously enlarged (see Fig 3.5)



Fig 3.—X ray of the knee joints of the child in Fig 3.6. Note the deposits in the epiphysis of the femur, the patella and the periarthritic tissues

prominent. There is moderate fever with a slight leucocytosis and frequently an elevation of blood pressure. The duration of the attack is from one to several days, as a rule recurring at intervals of months or years.

**Chronic Gout**—Chronic gout differs from acute gout in that with recurring attacks *tophi* and *bony changes* develop that leave a permanently damaged joint. There may be a chronic stiffness or a mechanical interference with mobility. Frequently bursae become chronically thickened and may even contain crystals of sodium monourate. Such cases may have multiple joints involved, the hands elbows knees ankles etc.



Fig 38—A ray of the foot in a case of chronic gout showing extensive destruction of the metatarsal and phalangeal bones and the articular surfaces particularly the great and little toe.

In addition to the arthritic signs of gout there is an irregular collection of conditions which are attributed to the so called *gouty diathesis*. They are found in members of gouty families who do not necessarily have arthritis. The principal manifestations are eczema with fine silver white scales similar to psoriasis which indeed may be also present. There are frequently attacks of biliousness or dyspepsia with a foul breath furred tongue constipation and an enlarged and tender liver. Migraine myalgias neuralgias sciatica



Fig. 36—A child suffering from scurvy. It is important to note the edema of the face, the atrophy of the limb, the tip of the fingers and the knees which are conspicuously enlarged (see Fig. 35).



Fig. 32—X-ray of the knee joints of the child shown in Fig. 36. Note the deposit in the epiphysis of the femur, the patella, and the periparticular tissues.



An acute inflammatory thickening of the metatarsophalangeal joint of the great toe is very characteristic of gout being the first symptom in a high percentage of the cases. This is largely a periarticular involvement due to deposition of sodium monourate crystals in the tissues. A thickening of the prepatellar and olecranon bursae may be found.



Fig. 330



Fig. 331



Fig. 332

Fig. 330—Photograph showing typical inflammation of chronic gout.  
 Fig. 331—Photograph showing typical inflammation of chronic gout.  
 Fig. 332—Photograph showing typical inflammation of chronic gout.

The blood uric acid is raised in acute gout (4 to 8 m<sub>g</sub>. per cent in whole blood and 6 to 12 m<sub>g</sub>. in serum) and the excretion of uric acid in the urine is increased. In chronic gout the blood uric acid may be normal or slightly raised as it will be in intervals between acute attacks.

Radiograms of the involved joints are of help. Clear areas due to bone absorption frequently occur in the epiphyses but they are not considered to be diagnostic unless they are 5 mm. or more in diameter.

and other vague but definite pains are common, as are also cramps in the legs. Iritis, iridocyclitis, and keratitis have been described, and are attributed to deposits of uric acid or its salts. Nephroliths composed of uric acid are not infrequent.

**Diagnosis**—The early diagnosis of gout is not easy since the one finding, tophi, that makes the diagnosis certain, does not develop as a rule until five to ten years have elapsed. During this interval arthritic pains about joints, cyclic in occurrence, may be the only symptom. Examination of the blood for uric acid will usually show it to be raised (above 4 mg. per cent in whole blood and 5 mg. per cent in serum). Therapeutic trial with colchicum is helpful.

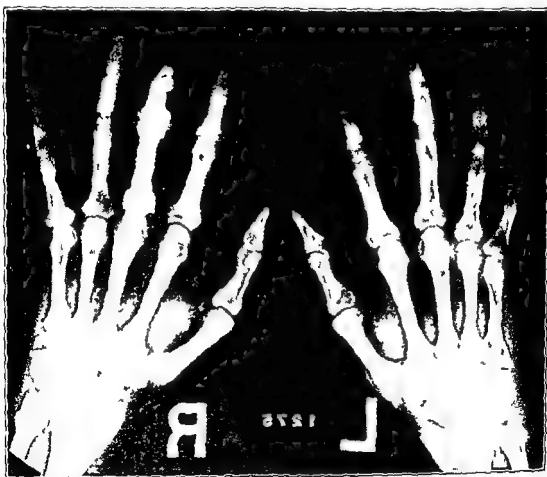


Fig. 39.—X ray of the hand in case of chronic gout showing destruction of the metacarpal bone of the first metacarpal, the first ring finger and the middle phalanx joint of the right middle finger.

Later on the tophi develop. They occur on the helix of the ear or about the affected joints, fingers or toes. They vary in size from a pinpoint to a large marble, and are whitish in color. Over the larger ones the skin is frequently ulcerated. These tophi are collections of sodium monourate crystals, and their exact identification depends upon the demonstration of the characteristic needle-shaped crystals under the microscope.

An acute inflammatory thickening of the metatarsophalangeal joint of the great toe is very characteristic of gout being the first symptom in a high percentage of the cases. This is largely a periarticular involvement due to deposition of sodium monurate crystals in the tissues. A thickening of the prepatellar and olecranon bursa may be found.



Fig. 30



Fig. 31



Fig. 32

Fig. 30—First metatarsophalangeal joint in a case of chronic gout.

Fig. 31—First metatarsophalangeal joint in a case of acute gout.

Fig. 32—First metatarsophalangeal joint in a case of chronic gout.

The blood uric acid is raised in acute gout (4 to 8 m. per cent in whole blood and 6 to 12 m. in serum) and the excretion of uric acid in the urine is increased. In chronic gout the blood uric acid may be normal or slightly raised as it will be in intervals between acute attacks.

Radiograms of the involved joints are of help. Clear areas due to bone absorption frequently occur in the epiphyses but they are not considered to be diagnostic unless they are 5 mm. or more in diameter.

and other vague but definite pains are common, as are also cramps in the legs. Iritis, iridocyclitis, and keratitis have been described, and are attributed to deposits of uric acid or its salts. Nephroliths composed of uric acid are not infrequent.

**Diagnosis**—The early diagnosis of gout is not easy since the one finding, tophi, that makes the diagnosis certain, does not develop as a rule until five to ten years have elapsed. During this interval arthritic pains about joints, cyclic in occurrence may be the only symptom. Examination of the blood for uric acid will usually show it to be raised (above 3 m. per cent in whole blood and 5 m. per cent in serum). Therapeutic trial with colchicum is helpful.

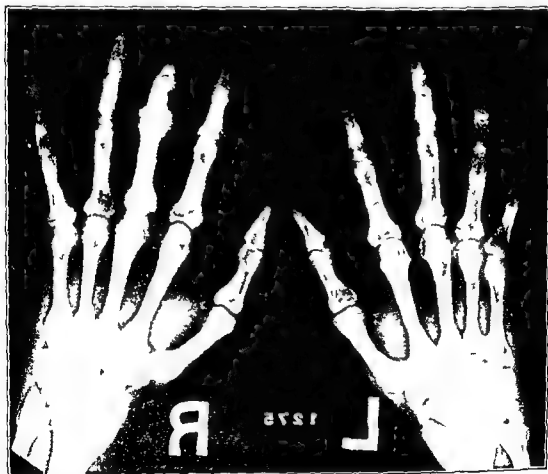


Fig. 39.—X-ray of the hands in case of chronic gout showing destruction of the metacarpal bone of the little finger and the middle phalangeal joint of the right middle finger.

Later on the tophi develop. They occur on the helix of the ear or about the affected joints, fingers or toes. They vary in size from a pinpoint to a large marble, and are whitish in color. Over the larger ones the skin is frequently ulcerated. These tophi are collections of sodium monourate crystals, and their exact identification depends upon the demonstration of the characteristic needle-shaped crystals under the microscope.

An acute inflammatory thickening of the metatarsophalangeal joint of the great toe is very characteristic of gout being the first symptom in a high percentage of the cases. This is largely a periarticular involvement due to deposition of sodium monourate crystals in the tissues. A thickening of the prepatellar and olecranon bursae may be found.



Fig. 30



Fig. 31



Fig. 32

Fig. 30—First metatarsophalangeal joint in a case of chronic gout.

Fig. 31—First metatarsophalangeal joint in a case of chronic gout.

Fig. 32—First metatarsophalangeal joint in a case of chronic gout.

The blood uric acid is raised in acute gout (4 to 8 m. per cent in whole blood and 6 to 12 m. in serum) and the excretion of uric acid in the urine is increased. In chronic gout the blood uric acid may be normal or slightly raised as it will be in intervals between acute attacks.

Radiograms of the involved joints are of help. Clear areas due to bone absorption frequently occur in the epiphyses, but they are not considered to be diagnostic unless they are 5 mm. or more in diameter.

The use of a purine test meal (100 grams of sweetbreads) given with breakfast, is thought to be of diagnostic help. Subsequently the blood uric acid is determined at six, twelve, and twenty four hour intervals. Normally it should have returned to the fasting value in twelve hours at the latest. This procedure tests the ability of the kidneys to excrete uric acid.

A further diagnostic test that has been suggested by Locke and Hubbard is the feeding of a high fat, low carbohydrate diet to be followed by a low fat high carbohydrate diet. Normal people develop a slight rise in their blood uric acid with high fat feeding, but with a low fat diet it rapidly returns to the normal value. In the case of gouty patients, the blood uric acid rises with the high fat diet much the same as in normal patients but with the low fat diet the return to the initial level is much delayed.

Gout in its early stages, especially before localization about a joint, is frequently not recognized, and the patient is treated symptomatically. Shifting joint pains, baelache, recurring attacks of lumbago without satisfactory cause should suggest the possibility of gout. When there is a localization in or about a joint its differentiation from the various types of arthritis has to be considered. The rheumatic fever joint is a fairly clearcut entity occurring in young individuals and usually involving multiple joints. The joints of rheumatoid arthritis may offer considerable difficulty, but the deformities x ray changes changes in skin temperature and sweating, and failure to clear up completely are significant. The characteristic gouty joint is swollen, red dened with marked sensitiveness of the surrounding skin. There may be mild degrees of lymphangitis in acute attacks, but there is little systemic fever. As the attack subsides all evidences of inflammation disappear. In chronic gout permanent joint changes are found with tophi. In doubtful cases of arthritis therapeutic trial with colchicum is helpful. While giving prompt relief in gouty arthritis it has little effect in the joints of acute rheumatic fever or rheumatoid arthritis.

**Complications**—In gouty individuals there is a tendency for systemic sclerosis of the arterial tree to develop at an early age. This may involve the arteries about the affected joints to a marked degree, seemingly interfering with their nutrition and leading to marked osteoarthritic changes. It has been stated that hypertension may occur in gout. There is also evidence to strongly suggest that this functional derangement may become permanent and lead to the cardiovascular renal changes described under Hypertension. Primary contracted kidneys are a common sequel in gout, hypertension, and lead poisoning. Rarely do patients die of gout itself but the outcome depends upon the rapidity of development of the systemic vascular disease. Many die in a terminal uremia.

**Treatment**—*The Acute Attack*—In the acute attack the joint involved usually the great toe is extremely tender. It should be protected from jars and drafts. Colchicum or its alkaloid colchicine should be given to a physiological effect and the diet should be free from purine yielding foods.

**Dietetic**—The diet should be regulated in two particulars. First the total caloric intake must be maintained at a level compatible with a normal weight. Those individuals overweight should be slowly reduced provided

there is no specific contraindication. This means a total caloric intake from 1800 to 2200 calories per day, according to age, sex, height, and activity of the patient.

Second, care must be taken to control the intake of nucleoprotein which yields the purine substances that are converted into uric acid. These foods are meat, fish, chicken, and all internal organs. Fruits, vegetables, milk, eggs, cheese, nuts, butter and bread are purine free. The nonprotein calories should be given largely as carbohydrate since fat tends to raise the blood uric acid. Condiments and spices should be avoided for they stimulate the appetite. Alcoholic beverages especially fermented liquors such as wines, beer and ale should be strictly forbidden.

The use of water should be encouraged in the acute stage up to 4000 cc per day. No special value has ever been proved for mineral water of any kind.

In the acute phase of the disease a strict observance of a purine free diet is advisable for three to four weeks after which meat, or chicken or fish can be allowed once a day. All purine rich foods should be permanently avoided.

In the chronic cases some liberty can be permitted as to the purine intake but a permanent restriction helps to prevent future acute exacerbations.

**Medicinal**—Colchicum and its alkaloid colchicine are by far the most useful and safest drugs in the treatment of gout. In large doses they relieve the pain of the acute attack and increase the excretion of uric acid in the urine. The alkaloid colchicine is thought to be more stable and therefore preferable. In the acute attack a dosage of 1 mg. for four doses at hourly intervals is usually sufficient to relieve the pain. Subsequently two to three doses of 1 mg. each per day are required for several days. If the wine or tincture of colchicum are used, a dosage of about 2 cc per day is necessary. This can be continued for several weeks. Since the wine and tincture of colchicum vary considerably in physiological activity the alkaloid is to be preferred. The symptom indicating toxicity from colchicum is diarrhea. A mild looseness of the bowels is not contraindicated as it indicates that a full physiological effect has been obtained. This is desirable.

Other drugs such as atophan, cinchophen and tolysin have been extensively used but their use is not without some danger. In the case of cinchophen toxic necrosis of the liver has been reported in several cases have been fatal. Sodium salicylate and aspirin are effective in increasing uric acid excretion but have no advantage over colchicum.

**Prophylaxis**—Those who inherit a gouty diathesis may possibly avoid an acute attack by taking care not to become overweight by avoiding excessive alcoholic consumption and by taking a fair amount of out of door exercise.

## OBESITY

Obesity is simply a state of being overweight. This excess weight is due to fat stored in the subcutaneous tissues, the omentum and other fat depots. If one exceeds his normal weight by more than 10 per cent he can be fairly stated to be mildly obese.

Fundamentally the specific cause of obesity is a greater intake of caloric yielding food than there is oxidation in the tissues. This positive balance in

stored as fat. One must remember that carbohydrate and fat have little specific dynamic action, and that the rate of oxidation in the cell is not appreciably influenced by food eaten. The amino acids of protein do cause an appreciable elevation of metabolism in periods of digestion through their specific dynamic

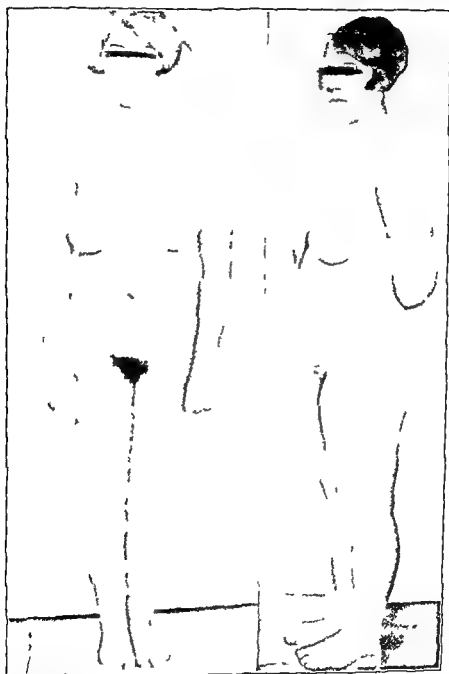


Fig. 33 A

Fig. 33 B

Fig. 33 A—Distribution of subcutaneous fat in a normal individual. Note the general distribution of the subcutaneous fat.

Fig. 33 B—Distribution of subcutaneous fat in an obese individual.

action but people become obese from excess consumption of carbohydrate and fat. Obesity develops in most people gradually and after being established interferes with physical activity thereby resulting in a vicious circle. It is to



be wondered if that more people do not become obese when one remembers van Noorden's calculation that an excess consumption of but 200 calories a day will result in a gain of 24 pounds in one year.

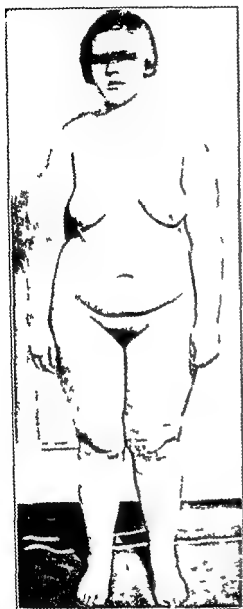


FIG. 234 A

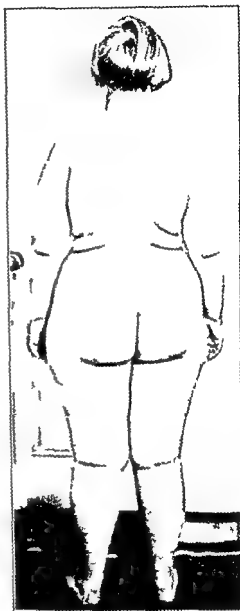


FIG. 234 B

Fig. 234 A—Frontal view of a woman with severe obesity, showing extreme enlargement of the breasts and abdomen.  
Fig. 234 B—Back view of the same woman, showing extreme enlargement of the buttocks and thighs.

**Pathological Anatomy**—Cases of obesity may be classified into exogenous or simple and endogenous. Exogenous obesity includes those cases where the gain of weight is due to excessive eating or decreased expenditure of energy, a normal basal metabolism being present. In endogenous obesity there is some

endocrine abnormality that results in a lowered rate of oxidation in the tissues which favors a gain in weight

**Exogenous Obesity**—Merris has shown in 41 cases that the basal metabolic rate is normal. In the Royal Victoria Hospital a woman with exogenous obesity weighing 385 pounds had a normal basal metabolic rate by the Sage standards. Studies upon their expenditure of energy when doing a known amount of work are not extensive enough to rule out the possibility that some cases of exogenous obesity produce less heat than the average normal. If this is proved, it may help to explain the gain of weight which at times is baffling. As shown by Plant and others the specific dynamic action of protein may be lessened or absent. This again would indicate that metabolic abnormalities which are not understood exist in at least some of these people. Further studies from the Royal Victoria Hospital have shown that in exogenous obesity a fatty acid glucose ratio of 3 to 1 in grams can be oxidized without a ketosis which again indicates a metabolic abnormality.

In the last analysis the gain or not of weight depends upon the ratio between the total caloric intake and the total metabolism, which is the basal metabolism plus the heat production referable to all physical activity and all endocrine excretants of heat production. Recent studies would strongly suggest that the phlegmatic temperament which is usually present in exogenous obesity may influence the total metabolism sufficiently to conserve 100 to 200 calories a day.

The tendency in obesity for the tissues to hold water is striking. This water retention must be intracellular because there is no pitting edema. Whether there is an associated base retention is not known.

**Endogenous Obesity**—Endogenous obesity differs from the exogenous in that there is a lowered rate of oxidation in the tissues due to an endocrine influence. This influence falls usually into one of three types: hypothyroidism, hypopituitarism, or hypogonadism. In hypothyroidism the fat deposits are characteristically located about the face and neck with the development of the so called 'moon face'. Frohlich's syndrome known as *dystrophia adiposogenitalis* is typical of pituitary obesity. The fat is in excess about the abdomen, hips, and thighs, the well known girdle obesity. The obesity characteristic of hypogonadism is well shown in eunuchs, women after the menopause, and in castrated animals. The deposition is usually general, and in women the lower leg becomes heavier.

**Symptoms**—The symptoms referable to exogenous obesity are in proportion to the degree of obesity. Early cases have no symptoms. More marked ones would complain of dyspnea and palpitation upon exertion. In the very marked cases moderate dyspnea may be present even at rest and activity is associated with so much discomfort that it is practically inhibited.

In endogenous obesity symptoms characteristic of the endocrine disturbance would be present as well as those referable to the obesity.

**Diagnosis**—The diagnosis is made by a comparison of the body weight with the standard weight for height, age, and sex. A deviation of plus or minus 10 per cent should be allowed as physiological. The basal metabolic rate determination helps to differentiate exogenous from endogenous cases.

A study of the diet history over an extended period of time may indicate an excess food intake. The most marked lowering of the metabolism is found in obesity with hypothyroidism. A moderately lowered metabolism is found in obesity with a pituitary or gonad basis.

**Prognosis**—Obesity of a marked degree if allowed to remain for an extended period of time materially affects the duration of life. Gradually and progressively systemic arteriosclerosis develops which is later associated with hypertension. Obesity also predisposes to hypercholesteremia which frequently results in gallstones with an associated cholecystitis. Infection of the gallbladder and biliary tract spreads by direct extension into the pancreatic duct with a resulting low grade pancreatitis and diabetes mellitus. So great is the frequency of diabetes in the obese that Joslin has estimated that an individual who is 10 per cent overweight is seven times more liable to diabetes than an individual 10 per cent underweight.

Acute respiratory infections such as pneumonia run a grave course in obesity. Eventually the excessive fat deposits conspire to embarrass the cardiovascular system. There is fatty infiltration of the myocardium, hypertension and a demand for increased cardiac work through increased peripheral resistance with resulting arterial changes (see under Hypertension). Obesity increases the surgical risk of major operations and there is greater danger of postanesthetic complications. The outlook and prognosis for the patient can be materially altered if reduction can be successfully accomplished and maintained.

**Treatment**—The fundamental concept in the treatment of obesity is to cause the patients to oxidize their own excess fat deposits by supplying a total caloric intake less than their total caloric expenditure. The intake has accordingly to be a subcaloric diet while the heat production can be influenced by exercise, hydrotherapeutic measures and by drugs in special cases. No short cut measures are wise or completely safe in the reduction of the obese. Along with the above a great desire and determination to follow directions or self discipline is essential on the part of the patient.

Exogenous obesity responds to treatment much more readily than endogenous obesity. Accordingly one must be very guarded in the prognosis to individuals with marked obesity on an endocrine basis. It is not safe to attempt reduction in all cases of obesity, either exogenous or endogenous. Those individuals showing degenerative changes with myocardial enlargement do not tolerate reduction well. In imminent failure of cardiac compensation may be made acute by too heroic measures.

Rapid reduction by a very low diet 500 calories per day is not wise because it is associated with a loss of body nitrogen, a fall in blood pressure, weakness and a greater tendency for the weight to be regained subsequently. A more gradual reduction with a diet of 70 to 90 grams of protein and 1000 to 1200 calories per day gives a much better result. The main part of the nonprotein calories should consist of carbohydrates with a minimum of fat. This avoids mild degrees of ketosis. Great care should be taken to include a minimal supply of inorganic salts and vitamins. The inorganic salt requirement in the main can be met by calcium phosphate supplemented by other elements.

as needed. Kelp tablets which contain a variety of inorganic elements have been used to advantage. The diet is usually rich in vitamin C due to its content of fruit juices. Vitamins A, B, and D will be low, and can be given in concentrated form. The choice of protein should be varied, including meat, fish and eggs so that all essential amino acids are included.

Fluid restriction of a moderate degree, 1200 cc per twenty four hours, is helpful and does no harm. Salt restriction, which no doubt accelerates weight loss, is widely employed, but in the writer's experience has at times resulted in a fall of the blood sodium with hypotension. Therefore if practiced, the blood pressure should be watched carefully.

Weight loss should not proceed at a greater rate than 2 pounds a week. Rarely is the weight loss uniform but it takes place at recurring intervals between which are plateaus of a few days' duration, due to water retention. Such periods of water retention can sometimes be overcome by a mild diuretic or by a day of rest in bed during which there will be a marked diuresis.

Exercise, guarded according to the case, is of great help, and makes for a more uniform loss of weight. This can be supplemented by general hydrotherapy and massage.

The only drugs that have a place in reduction, act through stimulating the rate of cell oxidation. The drug most widely used is thyroid extract. In exogenous obesity with a normal basal metabolic rate it should not be used until with the loss of weight there is a moderate fall in the basal metabolic rate. Then it can be used in small doses, sufficient to raise the basal metabolism to normal. However it must be remembered that protracted administration of thyroid extract tends to suppress thyroid function.

In endogenous obesity thyroid products can be wisely used in sufficient dosage to correct the hypothyroid state. Such patients are frequently very tolerant to large doses of thyroid gland. The writer has seen such cases where 30 grains of thyroid gland (Burroughs Wellcome) per day only raised the basal metabolic rate 1 or 2 per cent. The best results from thyroid therapy are obtained in obesity associated with myxedema.

Due to the difference in physiological activity of various thyroid products care should be taken definitely to specify the product upon the prescription. The iodine content of a thyroid preparation or extract is taken as the index of its biological activity. Although this is not exactly true it is the accepted standard. Different preparations however contain differing amounts of iodine. The following example will illustrate this. Burroughs Wellcome produces for use in Canada and Great Britain a thyroid extract which contains 0.3 gm per cent of iodine according to the I. P. requirement. But they produce for use in the United States a thyroid extract containing 0.2 gm per cent of iodine (0.17 to 0.23 gm) to meet the U. S. P. standards. Parke Davis also produces for use in Canada a thyroid extract containing 0.3 gm per cent of iodine to meet Canadian standards but this is known in the U. S. A. as "thyroid extract strong" to distinguish it from the standard U. S. P. extract containing 0.2 gm per cent of iodine. It will therefore be seen that there are two official preparations of thyroid extract used on this continent which vary in strength by 50 per cent iodine content.

Other drugs such as dimetrophenol whose specific effect is to raise the metabolism or oxygen consumption are dangerous and should be used only with the closest supervision. In the course of reduction a moderate anemia can be corrected by iron preparations. At infrequent intervals a saline cathartic helps to remove retained tissue fluid.

## LIPOMATOSIS

A lipoma is a localized collection of fat in fat cells. They occur in areas where fat is normally stored and may be unilateral or symmetrical. The nodular lipomas are encapsulated and are classified as nonmalignant tumors.

In addition to the circumscribed nodular accumulations of fat a diffuse deposition may be found which again may be symmetrical in its location. No definite disorder of fat metabolism has been discovered in these cases and a chemical analysis of the fat has shown no abnormality. This diffuse deposition is not a clinical entity but usually occurs in other diseases.

For the purpose of clarification a simple classification is best and helps to differentiate these states from the fat accumulations in obesity.

**Clinical Types**—1 *Nodular circumscribed lipomatoses* are not unusual especially in females. They cause no symptoms as a rule unless located in a position where they mechanically interfere with function. They may be lobulated and tender upon palpation. Rarely they cause disfigurement which justifies surgical removal.

2 *Diffuse symmetrical lipomatoses (adenolipomatoses)* are nonencapsulated collections of fat which usually are symmetrical, more common in males and involve the neck or shoulder regions. The degree of fat accumulation may be so great as to produce great disfigurement. Frequently there is a symmetrical collar of fat at the base of the neck in the supraclavicular regions. Symptoms rarely result. Not infrequently scattered throughout the fatty tissue are found small nests of lymphatic glands and more rarely hemolymph glands which justifies the term *adenolipomatosis*.

3 *Adiposis dolorosa (Dercum's disease)* is characterized by symmetrical nonencapsulated fatty deposits which are accompanied by pain, asthenia and mental instability. They are much more common in women than men and appear especially at the menopause. The abdominal wall, chest, arms and legs may be involved and the skin overlying the fatty deposits is usually hyperesthetic. Marked weakness is common. This disease tends to run a chronic course and is characterized by remissions.

4 *Adipositas cerebralis*—Lesions of the brain may indirectly be the cause of obesity of the endogenous type. These fat accumulations have a localized distribution which would justify their mention under lipomatosis.

For years Frohlich's syndrome or *dystrophia adiposogenitalis* has been connected with a pituitary dysfunction with little evidence to justify such an assumption. The delayed development of the secondary sexual characteristics might well be related to lack of the gonadotropic factor of the anterior

lobe of the pituitary, but the cause of the associated girdle obesity is still unexplained. Similar types of obesity have been related to lesions of the floor of the third ventricle.

5 *Lipomatosis associated with the pseudohypertrophic form of muscular dystrophy* is well known in this form of muscular lesion and may lead to apparent marked enlargement of special muscle groups due to extensive fatty infiltration of the muscles themselves. These muscles are functionally much impaired.

6 *Lipodystrophia progressiva* is a rare disease starting in childhood, and characterized by a marked emaciation with loss of subcutaneous tissue over the upper half of the body and a disfiguring obesity of the lower half. It is confined to females.

**Treatment**—Treatment of all these conditions must be rational. Surgical removal of the fatty tissue may be justified for cosmetic reasons. In those cases where there is an endocrine basis with a lowered basal metabolic rate thyroid products can be wisely used. Pituitary preparations by mouth have never been proved to have a physiological effect.

## HEMOCHROMATOSIS

Hemochromatosis (bronze diabetes) is a disorder of metabolism characterized by the deposition of large quantities of the iron-containing pigment hemosiderin, in the glandular organs. There is an associated pigmentation of the skin. This pigment deposition especially involves, and is associated with, a sclerotic process in the liver, pancreas and spleen. Glycosuria and hyperglycemia are so frequently present that the term bronze diabetes is often used. The syndrome was originally described by von Recklinghausen. No specific cause is known and its fundamental nature is uncertain but there would appear to be a defective excretion of iron.

The onset is insidious, as usually the diabetic state is first recognized. In time the skin pigmentation with enlargement of the liver and spleen lead to a tentative diagnosis which is confirmed as the disease progresses. The diabetic state increases in severity requiring larger and larger amounts of insulin. Malaise, loss of weight, and asthenia follow. The duration of the disease is usually a matter of months rarely a few years, after it has been recognized.

The anatomic pathological changes are characterized by deposition of pigments in the tissues with fibrotic changes as well as a moderate degree of cellular degeneration in parenchymatous organs. The liver and spleen are enlarged from the sclerotic changes and contain large quantities of hemosiderin. The liver has been found to contain as much as 38 grams of iron (the whole body normally contains 3 grams). The copper content of the liver has also been found to be increased (140 mg per kilogram). The significance of this copper retention has not been evaluated. The pancreas is usually small and fatty, with varying degrees of fibrosis. The islands of Langerhans may show degenerative changes. Alterations in the parenchymatous cells do not appear to be important but at times the pigment would seem to be causing

direct mechanical damage. Hemofuscin, a noniron containing pigment, is found especially in smooth muscle as well as in the heart muscle. This pigment contains sulfur, 37 per cent and is related to the melanins.

The diagnosis is frequently not made until autopsy. The presence of generalized bronze pigmentation of the skin associated with an enlarged firm liver and spleen should suggest the possibility. These findings in a male of middle age with an associated diabetic state would certainly justify a biopsy of the skin. Special staining methods show the hemosiderin which settles the diagnosis. The blood iron is not increased. Hemochromatosis may occur without diabetes. Males are much more frequently affected than females. The incidence is about 20 to 1. In a series of 311 cases reported in 1934 the youngest was aged twenty years while the maximum incidence was in the age period between forty five and fifty five years.

Pigmentation of the skin becomes deeper and the liver and spleen larger as the disease progresses. The associated diabetic state if present may become worse and require increasing amounts of insulin to control the defective carbohydrate metabolism. There sometimes develops a certain degree of insulin insensitivity. A moderate hyperbilirubinemia may be found. Weakness gradually becomes conspicuous with a progressive loss of weight. In 1927 primary cancer of the liver was reported to be present in 12 out of 128 cases.

**Treatment**—Treatment is without avail to alter the course of the disease. Maintenance of weight is difficult due to the extensive liver damage. The diabetic condition should be handled in the usual way (see Diabetes Mellitus).

### OCHRONOSIS

This is a rare metabolic disorder characterized by a darkening of the cartilages, ligaments and fibrous structures everywhere throughout the body. The skin also develops varying degrees of pigmentation. There seem to be two groups of cases, one in which there is an associated alkaptonuria and the other in which there has been a prolonged external application of carbolic acid preparations. When there is an associated alkaptonuria the darkening of the above mentioned structures is due to alkapton formed in the tissues from homogentisic acid, a derivative of the amino acids tyrosine and phenylalanine. Why homogentisic acid, a normal intermediary product is so changed is unsolved. When carbolic acid is the etiological factor the derivative that stains the tissues is unknown.

In the first group where there is an associated alkaptonuria the condition is congenital and runs a chronic course. Several members of the same family may be affected and it has been known to carry through three generations. When associated with carbolic acid poisoning, the course may be more acute.

The well advanced case presents a characteristic picture of discoloration of the cartilages of the ears and nose with staining of the fibrous tissues and tendons of the knuckles, hands and feet. This discoloration may even be coal black in the cartilage of the nose. With its chronic course systemic arteriosclerosis is usually found. As the cartilages of the joints are involved

they undergo degenerative changes which gradually lead to osteoarthritic outgrowths arthropathies and deformities

**Diagnosis**—The diagnosis is not difficult. The discoloration of the cartilages, especially of the ear, which is best seen by transmitted light, is of great help. The urine, if homogentisic acid is present, causes brown stains on linen which are not removed by soap (alkali). Further the urine will turn brown to black upon standing, or by the addition of alkali. When carbolic acid is the causal agent, the history will reveal its prolonged use, usually to the surface of a chronic ulcer. However, one must remember that many with alkaptonuria show no staining of their cartilages. Excretion of homogentisic acid is increased by a high protein diet, especially when casein is present in large quantities.

**Treatment**—Treatment of the congenital types associated with alkaptonuria is of little avail. The excretion of homogentisic acid is lowered somewhat when the diet contains not more than 0.5 gram of protein per kilo body weight which, however, is below the minimal biological requirements. In the case of carbolic acid its discontinuance will gradually result in a lessening of the cartilagenous discoloration.

### References

- Campbell W. R. and MacLeod J. J. R. *Insulin Medicine* 3: 193, 1934.  
 Darcum F. A. *Three Cases of a Hitherto Unclassified Affection Resembling, in Its Grosser Aspects, Obesity but Associated With Special Nervous Symptoms*. *Adipositas Dolorosa* Am. J. M. Sc. 104: 521, 1892.  
 Evans E. and Savory J. M. *The Treatment of Obesity With Low Calorie Diet*. J. A. M. A. 97: 1063, 1931.  
 Folin O., Berglund H. and Derick, C. *The Uric Acid Problem*. J. Biol. Chem. 60: 361, 1924.  
 Gamble J. I. and Ross S. O. *The Factors in the Dehydration Following, Historic Obstruction*. J. Clin. Investigation 1: 403, 1931.  
 Gunther H. *Die Lipomatosen und ihre klinischen Formen*. Jena, 1920. Gustav Fischer.  
 Hall E. M. and Michay F. M. *Experimental Hepatic Pigmentation and Cirrhosis: Does Copper Poisoning Produce Pigmentation and Cirrhosis of the Liver?* Am. J. Path. 7: 52, 1931.  
 Hartmann A. F. and Elman R. *The Effects of Loss of Gastric and Pancreatic Secretions and the Methods for Restoration of Normal Conditions in the Body*. J. Exper. Med. 58: 181, 1922.  
 Hatch J. S., Vanzant F. R. and Monland R. *Basis for Early Differential Diagnosis of Gout*. Clinic. Comparison of 100 Cases Each of Gout, Rheumatic Fever and Infectious Arthritis. Tr. A. Am. Physicians 43: 317, 1929.  
 Howard C. I. and Mills F. S. *Ochronosis*. *Oxford Medicine* 4: 23, 1931.  
 Joslin E. P. *The Treatment of Diabetes Mellitus*. 4th ed. Philadelphia, 1931. Lea & Febiger.  
 McLester J. S. *Nutrition and Diet in Health and Disease*. 2d ed. Philadelphia, 1931. W. B. Saunders Co.  
 Mallory F. B. *Hemochromatosis and Chronic Poisoning With Copper*. Arch. Int. Med. 37: 336, 1926.  
 Oppenheimer B. S. and Kline B. S. *Ochronosis With a Study of an Additional Case*. Arch. Int. Med. 29: 73, 1902.  
 Peters J. P. and Van Slyke D. D. *Quantitative Clinical Chemistry—Interpretation*. Vol. I. Baltimore, 1931. Williams & Wilkins Co.



- Pratt J H Gout, Nelson Loose Leaf Medicine 3 37 1923
- Rabinowitch I M Foster J S, Fowler A F and Corcoran A C Clinical Experiences  
With Irotanase Zinc Insulin Can Med Assn J 35 239 1936
- Rowntree L G Studies in Diabetes Insipidus, J A M A 83 399 1924
- Warren S Pathology of Diabetes Mellitus Philadelphia 1930 Lea & Febiger
- Wilder R M Colver Lecture The Treatment of Obesity International Clinics 4 43rd  
series 1 1933
- Wilder R M A Primer for Diabetic Patients ed 5 Philadelphia 1934 W B Saunders  
Co
- Wilder R M Hyperinsulinism International Clinics 2 1 1913
- Wilder R M Allan F N Poner M H and Robertson H E Carcinoma of the Islands  
of the Pancreas Hyperinsulinism and Hypoglycemia J A M A 89 348 1927

## CHAPTER XIV

### DISEASES OF THE DUCTLESS GLANDS

L. H. MASOV, PH.D., M.D.

#### INTRODUCTION

In the preceding chapters it has been stated, and more often inferred that the animal organism is not a group of separate systems but a beautifully balanced and coordinated whole which functions in spite of numerous changes in its external and internal environment. Its response to these changes operates with a smoothness and rapidity which alone permits of its survival. It is true that if they are violent and extreme, a disastrous result may occur but on the whole the power of adaptation is astonishing. This indicates a flexibility of function which is governed by factors of the utmost delicacy. The role of the nervous system in this regulation is of great importance, but in addition there is a humoral control which depends upon "incretions" or 'internal secretions' of the ductless or endocrine glands. There is hardly a function of the body which is not influenced or regulated by one or more of them. Fetal development, birth, growth, sexual differentiation, development and senescence, mental activity and emotional responses are all guided by them. In addition nutrition, intermediary metabolism, digestion, cardiac, respiratory, renal, hepatic and hematologic functions are controlled through their influence. The interrelations of the nervous system and the endocrine glands are of the greatest importance and the more that is known the more intimate and complex they become.

It must be emphasized at the outset that our knowledge of what is commonly known as endocrinology and in a broader sense neuroendocrinology is a subject of comparatively recent date. It is true that a fragmentary appreciation that these glands played a role in regulating the organism was suspected and there was considerable theoretical speculation concerning their function. This was to some extent clarified by experimental methods through glands being removed from animals and the deprivation effects noted. This was a pronounced step forward but when translated to the syndromes met with in clinical medicine it led to an era of the wildest and most unwarranted conclusions which continue to do much to discredit and hamper the progress of this branch of medicine. The introduction of biochemical methods and steroid chemistry was required to bring sanity after this era of unjustifiable speculations and conclusions and even yet this has not been completely successful. Pituitrin and adrenalin were discovered in the final years of the last century but twenty years had to elapse before further progress was made while during the past twenty years the medical world has become almost blasé by the rapidity of new discoveries in this field. It has not prevented speculation and premature conclusions outstripping facts. Pavlov has placed first in his bequest to the academic youth of Russia—

'Gradualness, gradualness and gradualness! In no sphere of medicine is this more necessary than in endocrinology. We live in an age of speed but this will not hasten Truth to disrobe herself!'

The continued and critical investigations in this field have demonstrated that the secretions of the ductless glands do not act as a simple cause and effect. They are to a certain extent interdependent in that it is through a balance of interaction that a smooth equilibrium is maintained. Further, one gland may not only have what appear to be specific functions of its own but it may also through separate actions either stimulate or retard the function of other glands or organs after a specific manner. This is particularly the case in regard to the pituitary gland which is increasingly being found to occupy a key position in this widespread regulation. Its close anatomical and neurogenic connection with the diencephalon where are situated so many centers of fundamental importance would suggest that there is every reason to suppose that the future will reveal an even greater association along both humoral and neurological lines than is suspected at the present. This does not warrant however speculation becoming truth or hypothesis a fact.

Many cases will be met with in the practice of medicine where the principal features will indicate what has been taken to be an established clinical syndrome to which a definite name has been given. But as these cases are studied more thoroughly and critically there will emerge undoubted indications of perversions, excesses or reductions of other functions. Their recognition may not be difficult but the reason is by no means always explainable with our present knowledge. Therefore if all cases encountered in the practice of medicine do not fall into the groupings or clinical syndromes dealt with below it is because combinations and permutations which may arise from the disturbances of function of these glands are of extreme variety. It should be pointed out that most of the classical clinical patterns such as acromegaly, Simmonds disease, Cushing disease, myxedema, Addison's disease etc. were based upon extreme disturbances of function usually associated with serious and demonstrable anatomical lesions. Furthermore it was considered reasonable that the symptoms and signs were attributable only to the disorder of the gland principally involved. Physiologists would have viewed this concept with some dubiety. There were three concepts which were not given due consideration. First that there could be a quantitative glandular disturbance within the direction of increase or decrease. Secondly that there might be a multiplicity of activities inherent in each endocrine gland and thirdly that these activities could by affecting other glands or systems produce quantitative or qualitative results which were secondary to the functions of the original gland where the dominant lesion was situated. It was the failure to appreciate these interrelationships which led to many erroneous conclusions. It will be noted in the following pages that whereas a clinical syndrome was originally attributed to a lesion of one of these glands it may be imitated by a lesion in another gland through its primary positive or negative effect. This is particularly true of the pituitary gland but there are other instances such as the interrelationships of the gonads and suprarenals, the suprarenals and

the pancreas and the pituitary and the pancreas. Many of these seemingly interdependent imbalances require much more investigation before a full understanding can be reached. I C M

## DISEASES OF THE PITUITARY GLAND

### Introduction

**Anatomy**—The pituitary gland is developed embryologically by an upward growth of epithelial cells from the roof of the pharynx which come into contact with a downward extension from the diencephalic floor. The epithelial cells, of ectodermal origin, form the anterior lobe, while the glial cells, of diencephalic origin, compose the posterior lobe, and are attached to the mid brain by the infundibular stalk. Between the two lobes there is a thin layer of cells known as the pars intermedia. In the passage upward of the epithelial cells of buccal origin, a tube of cells is formed, which usually becomes obliterated after contact has been made with the diencephalic down growth. If these cells persist they may lead to cyst formation and the craniopharyngiomas. Eventually the pituitary gland comes to rest in its bony fossa, the sella turcica, and is connected with the midbrain by its infundibular stalk which pierces the diaphragm of the sella. The normal pituitary gland measures about  $6 \times 10 \times 14$  mm.

Early in fetal life the epithelial cells of the anterior lobe differentiate into granular cells which take a stain readily, and are called chromophil cells and those which have a clear cytoplasm, take a stain poorly and are known as chromophobe cells. Later the chromophil cells develop either eosinophilic or basophilic granules. Normally about three quarters of these cells are eosinophilic and one quarter basophilic. The cells of the posterior lobe are of glial origin and are connected with the hypothalamus by unmyelinated nerve fibers passing along the infundibular stalk. The secretions of the anterior lobe of the pituitary are emptied directly into the blood stream while those of the posterior lobe may in part pass into the ventricular circulation of the brain.

**Physiology**—Our understanding of the physiology of the pituitary gland is largely based on observations upon the white rat. This animal is readily susceptible to hypophysectomy which makes it an ideal preparation for experimental trial with various hormone extracts. Fortunately the pituitary hormones are not species specific; thus experimental trial and therapeutic use are possible.

At present our knowledge of the pituitary hormones may be tabulated as follows:

#### A Anterior Lobe

- 1 Growth hormone (chromophil cells)
- 2 Gonadotropic hormones
- 3 Thyrotropic hormone
- 4 Adrenotropic hormone
- 5 Lactogenic hormone
- 6 Diabutogenic hormone

## B Posterior Lobe

### 1 Pituitrin

Pressor action

Oxytocic action

Antidiuretic action

The *growth hormone* is produced by the eosinophilic cells of the anterior lobe. It controls normal growth and development of the skeleton and viscera. If produced in excess as in the case of the eosinophilic adenoma, gigantism results if the epiphyses of the long bones have not united, and acromegaly if they have united. The *gonadotropic hormones* are the follicle stimulating hormone (FSH) to the ovary with resulting estrin production. In the male it stimulates spermatogenesis. The other gonadotropic hormone is the luteinizing hormone (LH) which in the female stimulates the thecal cells of the ovary to produce the corpus luteum hormone. In the male it stimulates the interstitial cells of the testes to produce the male hormone (testosterone). Thus the gonadotropic hormones control estrin production and indirectly the menstrual cycle in the female and spermatogenesis in the male. Also they influence the characteristic secondary sexual development in both sexes. The *thyrotropic hormone* influences the function of the thyroid gland. If deficient a state of secondary hypothyroidism will develop. If excessive hyperplasia of the thyroid with a raised metabolism follows. In animals this hyperplasia is limited by the development of an antithyrotropic substance. The *adrenotropic factor* acts upon the cortex of the adrenal. If lacking atrophy of the adrenal cortex occurs. The *lactogenic hormone* (prolactin) influences milk secretion. The *diabetogenic hormone* (VPI of Young) has as yet been insufficiently investigated in man. In fact there is considerable diversity of opinion as to whether it acts in a direct manner upon carbohydrate and protein metabolism or whether VPI contains some corticotropic hormone which stimulates the adrenal cortex to overactivity which then stimulates the liver to produce hyperglycemia. The specific cell of the anterior lobe that makes these hormones is only known in the case of the growth factor.

Extracts of the posterior lobe have a marked pressor action upon the blood pressure probably through the intermediary action of the adrenal gland. The oxytocic action upon the pregnant uterus is well known. Intestinal tone and peristalsis are also influenced by this factor. The exact mechanism of the antidiuretic effect of the posterior lobe extracts is not known. Therapeutically this factor (antidiuretic) is employed in the treatment of diabetes insipidus.

**Experimental**—Removal of the posterior lobe causes little effect. Complete removal of the hypophysis in the immature white rat results in infantilism comparable to the infantilism of a child occurring after destruction of the pituitary by a craniopharyngioma. Such animals can be made to grow and develop by daily transplants of fresh exogenous hypophyseal tissue. In the mature white rat removal of the hypophysis results in immediate cessation of estrus in the female and genital atrophy in the male. The animals lose weight become sluggish and their basal metabolic rates fall to minus 35 per cent or more. Atrophy of the thyroid, parathyroid and suprarenal cortex follows. With transplant therapy improvement takes place.

In view of the tremendously widespread influence of the pituitary gland, it has been justly termed the "master gland." From birth to death its normal function controls, primarily or secondarily, the skeletal and visceral development, the rate of tissue oxidation of foodstuffs, the sexual transformation of puberty, and the reproduction of the species. The results of changes of pituitary function, as to either increase or decrease, can be fairly well postulated when they are present to a pronounced degree. However, much difficulty of assessment may be encountered when the disturbance is relatively moderate in degree, which may range over a wide realm. This is applicable whether the function is increased or decreased and may be further complicated by the relative secondary effects upon other glands, particularly the adrenals and the gonads.

### Hyperpituitary Function

**Gigantism**—Gigantism results from a state of hyperfunction of the anterior lobe of the pituitary. This hyperfunction is caused by a diffuse hyperplasia or a tumor development of the eosinophilic cells of the anterior lobe.



FIG. 33.—Photograph of a tall acromegaly and a pituitary dwarf standing beside a man of normal stature. (Courtesy of Dr. Hecor Morton.)

The tumor is of the adenomatous type and the hormone produced in excess is the growth factor. This disturbed function must develop before the epiphyses of the long bones have united to cause the great height characteristic of gigantism. There is an associated enlargement of the viscera and other organs.

Gigantism frequently starts at the time of puberty with a very rapid skeletal growth during the next few years. If a tumor is the cause, there may be headache and other symptoms referable to pressure upon the neighboring structures. An x-ray of the skull may show the presence of an expanding lesion in the sella turcica. Giants are not as strong as their size might indicate and their mental capacity may be below the average.

The excessive production of the growth hormone is frequently associated with a defective output of the gonad stimulating factor which results in sexual immaturity and delay in the closure of the epiphyses. This will extend the growth period into adult years. If the state of hyperfunction persists after growth has ceased the acromegalic syndrome will be superimposed upon that of gigantism. During the period of hyperfunction the gigantic state is progressive but as in acromegaly, a degenerative phase usually follows with a corresponding hypofunction. It is not unusual to find during the hyperactive phase indications of hyperactivity in the other ductless glands such as the thyroid, adrenal, pancreas and gonads. When this has become established the general health is greatly impaired and death follows from some complicating infection.

**Treatment**—Treatment consists of either surgical removal of the tumor if an adenoma and approachable or x-ray therapy. If x-ray treatment is instituted early there is a remote possibility of controlling the excess production of the growth hormone since the eosinophilic cells are sensitive to x-ray. The effect of x-ray therapy upon the production of the other hormones in the growing child is not well established.

### Acromegaly

Acromegaly is a disease syndrome referable to an excessive production of the growth hormone by the eosinophilic cells of the anterior lobe of the pituitary. If this hyperfunction develops before the epiphyses of the long bones have united gigantism results; if afterward, acromegaly. In most cases of acromegaly an adenoma composed of the eosinophilic cells is found, rarely is there a diffuse eosinophilic infiltration. The degree of development of the acromegalic state is directly proportional to the number of eosinophilic cells in the gland.

The typical eosinophilic adenoma is highly cellular, contains little connective tissue and the cytoplasm is coarsely granular. In time, areas of degeneration and hemorrhage passing on to necrosis develop in these tumors. With such degeneration the earlier state of hyperfunction passes into one of hypofunction with varying degrees of pituitary insufficiency.

**Symptoms and Signs**—In its early stages the excess production of the growth hormone is associated with an insidious enlargement of the hands and the feet. Not until it has been necessary to increase repeatedly the size of the gloves and the shoes is this enlargement called to the attention of the patient. At this time a degree of prognathism is usual. Progressively the skin becomes thickened and coarse, the palm of the hand broadens and the facial features coarsen and thicken. Friends may be the first to observe a change in appearance. The skull becomes enlarged with a great prominence of the supraorbital

In view of the tremendously widespread influence of the pituitary gland, it has been justly termed the "master gland." From birth to death its normal function controls primarily or secondarily the skeletal and visceral development, the rate of tissue oxidation of foodstuffs, the sexual transformation of puberty, and the reproduction of the species. The results of changes of pituitary function as to either increase or decrease can be fairly well postulated when they are present to a pronounced degree. However, much difficulty of assessment may be encountered when the disturbance is relatively moderate in degree which may range over a wide realm. This is applicable whether the function is increased or decreased and may be further complicated by the relative secondary effects upon other glands, particularly the adrenals and the gonads.

### Hyperpituitary Function

**Gigantism**—Gigantism results from a state of hyperfunction of the anterior lobe of the pituitary. This hyperfunction is caused by a diffuse hyperplasia or a tumor development of the eosinophilic cells of the anterior lobe,



Fig. 335.—Photograph of a pituitary giant and a pituitary dwarf standing beside a normal male (Courtesy of Dr. Hector Marston).

The tumor is of the adenomatous type and the hormone produced in excess is the growth factor. This disturbed function must develop before the epiphyses of the long bones have united to cause the great height characteristic of gigantism. There is an associated enlargement of the viscera and other organs.



quality, due to the anatomical alterations of the larynx and head. Exostoses are frequent about the terminal phalanges. Muscular strength is not in proportion to the hypertrophy of the organs.

Headache is usually an early symptom. As the tumor arises within the anterior lobe, increased tension is brought upon the diaphragm of the sella with the characteristic pituitary headache. With enlargement of the tumor the diaphragm of the sella may rupture with relief of this headache.

The eosinophilic adenoma in its early stages is associated with an excess production of the gonadotropic factor resulting in menorrhagia and an increased libido. If the tumor breaks through the diaphragm and extends upward pressure on the optic chiasm may occur with bitemporal hemianopsia and all degrees of optic atrophy. Pressure on the hypothalamic region will cause polyphagia, polyuria, and polydipsia. Glycosuria with hyperglycemia occurs in about one third of the cases of acromegaly and this diabetic state is usually resistant to insulin. Early in the tumor growth degrees of erosion of the sella turcica may occur. Ultimately this may involve all the clinoid processes and even extend into the sphenoidal sinuses. The x-ray picture is similar in this respect to that found with the chromophobe adenoma.

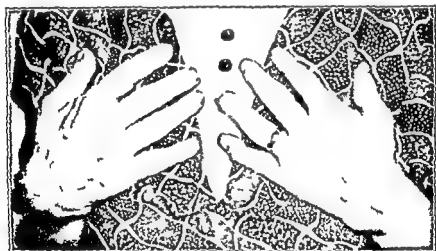


Fig. 333.—Photomicrograph of the adenoma (see Fig. 332).

Compression of the remaining pituitary tissue may result in all degrees of pituitary insufficiency. Amenorrhea in the female and impotence in the male indicate a defective gonadotropic function.

As the tumor undergoes degenerative changes, the state of hyperfunction is changed into one of hypofunction. Those skeletal and visceral changes that have already developed persist but muscular atrophy with looseness of the skin occurs with general weakness and asthenia. Hyperglycemia and glycosuria may revert to an increased carbohydrate tolerance.

**Treatment.**—The eosinophilic cells of the pituitary are sensitive to a ray. In its early stages before there is evidence of pressure on the optic chiasm intensive crossfire with x-ray may cause a shrinkage in the size of the adenoma.

ridges and mandible. The superior maxillary bones enlarge and the teeth become widely spaced. The air sinuses of the skull may develop to huge proportions. At this time there is a general macrosomia and macrosplanchnia which includes the tongue. Hypertrichosis, with a coarsening of the hair on the head, occurs. The sweat assumes an acrid odor, and the voice changes in



Fig 33f



Fig 33e



Fig 33d

Fig 33e—Photograph of a young man, taken at the time of his subsequent development of acromegaly.

Fig 33f—Photograph full face of the same patient as in Fig 33e, taken fifty-one years after acromegaly is well established.

Fig 33d—Profile photograph of the same patient as seen in Fig 33e.

of a basophilic adenoma which was proved at autopsy. Subsequently this syndrome has been described in considerable detail by Cushing, and on this continent it has been termed Cushing's syndrome.

The syndrome may occur in either sex, but is more frequent in women. It is characterized by (1) an adiposity of the trunk without involvement of the extremities (2) purplish abdominal striae (3) excessive growth of hair on the face (4) plethoric facies (5) hypertension, (6) a tendency for skeletal decalcification with fractures (7) secondary sexual characteristics in the female to revert to the male type (8) transient hyperglycemia and glycosuria and (9) erythrocytosis. Amenorrhea occurs in females. Rarely does an individual case present the complete syndrome.

The exact relationship of this syndrome to a basophilic lesion of the pituitary is not clear. Many basophilic adenomas have been reported without the syndrome and more recently the syndrome has been found without a tumor in the pituitary. Further this clinical syndrome has been found associated with malignant tumors of the adrenal cortex. In fact it would appear that this condition is in the way of being a hyperadrenocorticism either secondary to hypophyseal stimulation of the adrenal or due to a primary adrenal lesion (see page 940).

These tumors are not removable surgically. X-ray therapy has been followed by improvement in a few cases.

### Hypopituitary Function

**Vascular**—Deficient pituitary function secondary to a vascular lesion is not as rare as once thought. An inflammatory thrombosis of the vascular supply of the gland has been reported. This has usually followed an acute infection such as typhoid fever. There may be a partial or total cessation of pituitary function according to the circulatory impairment. Further the resulting states would be largely influenced by the period in life at which the complication developed. If total pituitary lack occurred in childhood an infantile dwarf would result.

**Postinflammatory**—Following infective processes varying degrees of pituitary insufficiency have been reported. These may be viewed as the end results of an associated inflammatory involvement of the pituitary gland with resulting fibrosis. The syndromes following are comparable to those found after interference with the blood supply of the pituitary gland and in certain cases of Simmonds' disease (Compression Syndromes see page 904).

### Frohlich's Syndrome (Dystrophia Adiposogenitalis)

*Frohlich's syndrome results from a deficiency of both lobes of the pituitary gland.* It is characterized by a bird-like type of obesity and sexual infantilism. The sexual immaturity is due to a deficiency of the gonadotropic hormone of the anterior lobe but the cause of the obesity is unknown. There is an associated increased carbohydrate tolerance and a moderate lowering of the basal metabolic rate. The picture is that of a quantitative reduction of pituitary function.

later after the diaphragm of the sella has ruptured, even when visual defects have developed, improvement in sight may follow this treatment. If the tumor is causing a progressive loss of sight, surgical intervention may become necessary. Since these adenomas are not encapsulated, their removal is difficult and not completely satisfactory. Acromegals are poor surgical risks from the point of secondary complications.



Fig. 340—X ray of the skull in a case of acromegaly, same case as Fig. 3. Note excessive enlargement.

### Basophilism

In 1903, Erdheim described two small tumors of the anterior lobe of the pituitary which were composed of basophile cells. These growths were of an adenomatous character but there was no associated clinical syndrome. In 1931, Teel from the clinical and laboratory findings diagnosed the presence

of a basophilic adenoma which was proved at autopsy. Subsequently this syndrome has been described in considerable detail by Cushing, and on this continent it has been termed Cushing's syndrome.

The syndrome may occur in either sex, but is more frequent in women. It is characterized by (1) an adiposity of the trunk without involvement of the extremities, (2) purplish abdominal striae, (3) excessive growth of hair on the face, (4) plethoric facies, (5) hypertension, (6) a tendency for skeletal decalcification with fractures, (7) secondary sexual characteristics in the female to revert to the male type, (8) transient hyperglycemia and glycosuria, and (9) erythrocytosis. Amenorrhea occurs in females. Rarely does an individual case present the complete syndrome.

The exact relationship of this syndrome to a basophilic lesion of the pituitary is not clear. Many basophilic adenomas have been reported without the syndrome, and more recently the syndrome has been found without a tumor in the pituitary. Further, this clinical syndrome has been found associated with malignant tumors of the adrenal cortex. In fact it would appear that this condition is in the way of being a hyperadrenocorticism either secondary to hypophyseal stimulation of the adrenal or due to a primary adrenal lesion (see page 940).

These tumors are not removable surgically. X-ray therapy has been followed by improvement in a few cases.

### Hypopituitary Function

**Vascular**—Deficient pituitary function secondary to a vascular lesion is not as rare as once thought. An inflammatory thrombosis of the vascular supply of the gland has been reported. This has usually followed an acute infection such as typhoid fever. There may be a partial or total cessation of pituitary function according to the circulatory impairment. Further the resulting states would be largely influenced by the period in life at which the complication developed. If total pituitary lack occurred in childhood an infantile dwarf would result.

**Postinflammatory**—Following infective processes varying degrees of pituitary insufficiency have been reported. These may be viewed as the end results of an associated inflammatory involvement of the pituitary gland with resultant fibrosis. The syndromes following are comparable to those found after interference with the blood supply of the pituitary gland and in certain cases of Simmonds' disease. (Compression Syndromes see page 904.)

### Frohlich's Syndrome (Dystrophia Adiposogenitalis)

Frohlich's syndrome results from a deficiency of both lobes of the pituitary gland. It is characterized by a girdle type of obesity and sexual infantilism. The sexual immaturity is due to a deficiency of the gonadotropic hormone of the anterior lobe but the cause of the obesity is unknown. There is an associated increased carbohydrate tolerance and a moderate lowering of the basal metabolic rate. The picture is that of a quantitative reduction of pituitary function.

**Symptoms and Signs**—The typical syndrome has its onset in the pre pubertal period. Rarely it is seen in adults. The obesity is marked about the pelvis and the lower abdomen while the arms and the legs remain normal. This is known as the pituitary type of obesity. The penis and the testicles are infantile, and at puberty there is a failure of development of the secondary

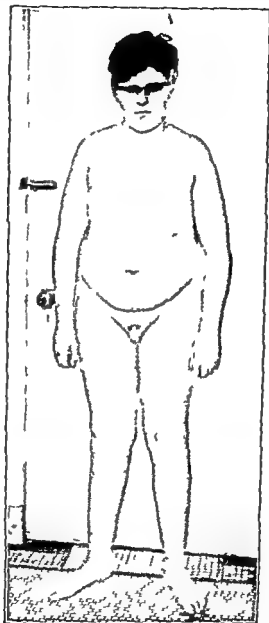


Fig. 341.—Photograph of the 'pitted type' of obesity in a boy of fifteen years. Note girth obesity, sexual immaturity, genital atrophy. Basal metabolic rate -1 per cent.

sexual characteristics. The voice remains high pitched in the male, and menstruation does not appear in the female. The syndrome having its onset before puberty may disappear with puberty. Care should be taken not to diagnose fat children, without due investigation as cases of hypopituitarism. Many such suspects at the time of puberty lose their obesity and sexual differentiation proceeds in a normal manner.

**Diagnosis**—The diagnosis before puberty is difficult. If puberty is delayed and the syndrome becomes more evident, the situation is clarified. The girdle obesity, the genital infantilism and the failure of the secondary sexual characteristics to develop, are the main features. The basal metabolic rate is lowered (minus 15 to minus 20 per cent) without signs of myxedema, and the carbohydrate tolerance is raised. Much is the evidence of an intra- or suprasellar cyst.

**Treatment**—The literature has reported improvement and cure with the oral use of pituitary preparations that we now know are physiologically inactive. The writer has likewise misinterpreted results but now has concluded that "nature" cured the patients at the time of puberty. However, today we have physiologically active preparations of the various hormones of the anterior lobe. Of these the ones that have given the best results as to growth and maturity have been in our hands a prolonged administration of A.P.L. and the maturity factor of the anterior lobe. The dosage has been 1 cc hypodermically of each preparation given on alternate days. In a young male with marked delay of sex maturity and growth (5 feet high) treatment was started at 17 years of age. His skeletal age was 13 years. After three years of treatment his height increased 6½ inches, his skeletal age was the same as his chronological age and the *sex organs* had reached normal development. The gonadotropic factor has been used with reported success. A word of warning is necessary at this point as all patients do not react satisfactorily, while in others the improvement may be so spectacular as to cast doubt on the correctness of the diagnosis. It is not unusual to see cases with puberty delayed beyond the expected age suddenly develop within a few months in a perfectly normal manner without any specific therapy. Therefore diagnosis and prognosis should be cautious.

### Simmonds Disease

In 1914 Simmonds described a state of progressive cachexia developing in an adult due to deficient function of the anterior lobe of the pituitary. The syndrome would indicate that all functions of this lobe are in abeyance. The anterior lobe of the pituitary may be destroyed by tumors, trauma and a variety of local intracranial lesions and has been associated with certain systemic conditions as widely diverse as phosphorus poisoning and hypertension. The syndrome has occurred in the prepuberal period from destruction of the anterior lobe by a craniopharyngioma. The most important group is that associated with parturition. Sheehan and Murdock have made an extensive study of these cases. They have found that the most common associated facts are a stormy birth with severe hemorrhage and sometimes infection. There occurs a necrosis of the anterior lobe which may vary widely in degree beginning from a small area on the anterior inferior portion under the capsule to a patchy distribution and often complete destruction. This is replaced either by fibrosis or a cyst. They have attributed the lesion to an arterial thrombosis, but the evidence is not conclusive.

The clinical picture in a florid case is most striking. There is progressive emaciation with asthenia. The average weight of the patients in the published

reports is 90 pounds. There is a general microsplanchma, that of the thyroid and adrenal being functionally most conspicuous. The changes in these two organs are essentially atrophy and not a destruction, as in myxedema and Addison's disease. In addition to the emaciation there is a wide range of symptoms

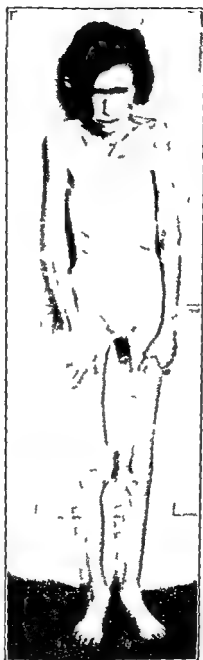


Fig. 342.—Photograph front view of a case of pituitary cachexia (Simmonds' disease) taken before adolecence.

and physical signs. They may complain of being always cold and shivering; there is mental depreciation; they are careless of their persons and habits and suspicious to a degree that may make examination and treatment impossible; in fact they may become definitely psychotic. The pubic and axillary hair



disappears the teeth may fall out the breasts uterus and external genitalia atrophy as do also the ovaries and testes. Libido disappears, and there is amenorrhea.

Examination shows a subnormal temperature, a slow pulse, slow respirations and a low blood pressure. The uterus is infantile and the breasts atrophic. The blood sugar is low varying on hypoglycemia and there is abnormal sensitivity to insulin. The basal metabolic rate may be minus 30 to minus 40 per cent. The writer has observed a case in a young woman with transient edemas causing a temporary gain of 20 pounds in weight. In the less florid cases all degrees of these symptoms may be encountered and in varying combinations. This is particularly so in cases following parturition.



Fig. 343.—X-ray of the skull of the case shown in Fig. 342. Note rotation of the supraorbital foramen.

It is very probable that many such cases are not recognized as due to partial pituitary destruction and cannot be rightly called Simmonds' disease in the sense that he originally described it. Emaciation is not always an essential feature of these milder cases; in fact increase of weight has been reported in the presence of other symptoms. As it may occur in both sexes in a modified degree these cases are not only associated with parturition.

The diagnosis of the extreme cases is not difficult but they must be differentiated from anorexia nervosa which however usually occurs in adolescence or soon thereafter. The general symptoms and signs are quite similar but the

mental disturbances are not. In anorexia nervosa there is often an antedating psychic insult usually of a sexual basis. Hysterical manifestations are more prominent than are those of a psychosis and they are quick and alert in their mental reactions. The diversity of the symptoms in this latter disease may be accounted for through the deleterious influence of starvation upon endocrine functions. The other diseases to be differentiated are hypothyroid function (myxedema) and Addison's disease. In the former the other endocrine deficiencies are not so evident, particularly those referable to the sex hormones.



Fig. 344.—Photograph side view of a young woman who took a prize at a beauty contest and subsequently developed anorexia nervosa.

In the latter the specific biochemical changes (see page 936) may give a lead and, if skin pigmentation is present it would eliminate the pituitary syndrome. It must be appreciated that the picture may be dominated by lack of growth, gonadotropic, adrenotropic or thyrotropic hormones or any combination thereof. But here is presented often a great problem in differentiation between a lesion of the adrenal cortex and of the pituitary particularly in those cases where the syndrome is only partially developed. The diagnosis may be helped, however, by the determination of the 17 ketosteroids and corticoids in

the urine the Kepler-Lowry water test and the Wilder sodium chloride test (see page 937). These may be further extended by the estimation of excretion of follicle stimulating hormone (FSH) to help assess the activity of the



Fig. 34.—X-ray of the pelvis of a woman in the 14th year after a hysterectomy, suggestive of pituitary disease. The pelvic bones are well developed, which were usually due to the normal development of the

pituitary gland. In the milder postpartum cases failure of lactation and amenorrhea should be viewed with suspicion as to the possibility of a pituitary lesion.

mental disturbances are not. In anorexia nervosa there is often an antedating psychic insult usually of a sexual basis. Hysterical manifestations are more prominent than are those of a psychosis and they are quick and alert in their mental reactions. The diversity of the symptoms in this latter disease may be accounted for through the deleterious influence of starvation upon endocrine functions. The other diseases to be differentiated are hypothyroid function (myxedema) and Addison's disease. In the former the other endocrine deficiencies are not so evident, particularly those referable to the sex hormones.



Fig. 344—Photograph illustrating a young woman who took a prize at a beauty contest and subsequently developed anorexia nervosa.

In the latter the specific biochemical changes (see page 936) may give a lead and, if skin pigmentation is present it would eliminate the pituitary syndrome. It must be appreciated that the picture may be dominated by lack of growth, gonadotropic, adrenotropic or thyrotropic hormones or any combination thereof. But here is presented often a real problem in differentiation between a lesion of the adrenal cortex and of the pituitary particularly in those cases where the syndrome is only partially developed. The diagnosis may be helped, however, by the determination of the 17 ketosteroids and corticoids in

the urine the Kepler Power water test and the Wilder sodium chloride test (see page 937). These may be further extended by the estimation of excretion of follicle stimulating hormone (F'SH) to help assess the activity of the



Fig. 34 —Front view of the same woman as in Fig. 33 after symptom suggestive of pituitary castration had developed which was really due to anorexia nervosa.

pituitary gland. In the milder postpartum cases failure of lactation and amenorrhoea should be viewed with suspicion as to the possibility of a pituitary lesion.

The course of the well established disease in the nonparturient cases is usually slowly progressive but may last for years. In the less conspicuous cases relative recovery sometimes occurs but in these the anatomical diagnosis is always in doubt.

**Treatment**—In the cases occurring after parturition it is claimed that if pregnancy can occur again by natural or artificial means almost complete recovery will take place provided the confinement is devoid of the original complications of hemorrhage and sepsis. Others have reported benefit from pregnancy urine and pituitary extracts, but it is difficult to be certain always that these are authentic results on account of the imitation of so many cases by anorexia nervosa. In cases with dominating thyroid deficiency thyroid therapy may be beneficial, and where hypoadrenal deficiency is prominent, cortin might be of value. But there are other functional fractions of the adrenal hormones dependent for their stimulus from the pituitary gland which must be taken into consideration. These are as follows: (1) the salt or electrolyte balance which must be preserved (see page 949) (2) the value of deoxycorticosterone acetate to meet certain specific deficiencies, (3) testosterone is sometimes of theoretical value and should not be neglected as a possible therapeutic agent to meet certain features of the disease (4) finally, it must be appreciated that through the complete absence of the adrenotropic hormone the so called adrenal deficiency crises may occur. These should be handled as laid down when the primary lesion is in the adrenal glands themselves (see page 940). J. C. M.

### Compression Syndromes

Syndromes resulting from compression of the pituitary gland may result from (1) craniopharyngiomata and (2) chromophobe adenomata.

#### Craniopharyngiomata

It will be recalled that in the process of development of the pituitary gland an epithelial upgrowth takes place from the roof of the pharynx to meet a diencephalic down growth. This epithelial stall forms the anterior lobe and in the process of its being pinched off, cell rests not infrequently remain which by growth and expansion form the craniopharyngioma tumors (Rathke's pouch tumors). These tumors may arise from cell rests above or below the diaphragm of the sella, and vary in size from a small pea to a good sized ball. They may be solid or cystic. Mature differentiation of the composing cells may follow producing cornification or keratohyaline changes. Again there is a great tendency for cystic degeneration with calcification of the walls. The cystic tumors contain an oily fluid with an abundance of cholesterol crystals. Strictly speaking craniopharyngiomata are not malignant but if they have invaded the grey matter there is no true capsule. On account of their position and size, all symptoms and signs are related to pressure effects. No hormone production has been observed. Their frequency is greatest in the second decade of life.

**Symptoms and Signs**—The earlier symptoms are usually headache and vomiting, most frequently occurring in a child who has shown varying degrees

of defective development. Further symptoms depend upon the pressure of the tumor upon contiguous structures. From pressure upon the anterior lobe of the pituitary all grades of defective growth and sexual differentiation may follow. It therefore should be emphasized that many of the signs and symptoms are to a large extent dependent upon the age at which pituitary deficiency manifests itself. This is true irrespective of the original cause. Pressure upon the optic chiasm leads to optic atrophy, bitemporal hemianopsia and complete bilateral blindness. Involvement of the hypothalamic region may result in polyuria, polydipsia and hyperosmotence. With occlusion of the aqueduct of Sylvius hydrocephalus will occur.

Physical examination will show the above symptoms in accordance with the structures involved. The temperature is usually subnormal, and the basal metabolic rate moderately lowered. Due to the frequency of calcification of the walls of the tumor x ray shows a shadow in approximately 80 per cent of the cases. Erosion of the sella turcica and an area in the base of the skull is variable.

**Treatment**—Treatment is surgical. If cystic withdrawal of the contained fluid will sometimes relieve the pressure symptoms for one to one and a half years. Total removal is extremely difficult. Medical treatment should be designed to correct deficient pituitary function, especially the lack of the growth and the gonadotropic hormones.

### Chromophobe Adenoma

The chromophobe tumors primarily arise from the epithelial cells of the anterior lobe of the pituitary in their early differentiation into chromophile or granular cells, and chromophobe or cells with a clear cytoplasm. The eosinophilic chromophile cells are known to produce the growth hormone, but no function has been proved to be carried on by the chromophobe cells. These cells have a marked tendency to form adenomata which are highly cellular and friable. They usually grow slowly and cause symptoms resulting from pressure upon the remaining pituitary tissue and the suprasellar structures. Erosion of the sella turcica may be marked with extension even into the sphenoidal air sinuses. While the craniopharyngiomata are commonest in early life the chromophobe adenomata develop in middle age. The sexes are equally affected. Like the craniopharyngiomata the symptoms depend on pressure upon the remaining pituitary gland or upon contiguous structures. Due to their development in a later age period the resulting syndrome may be markedly different.

**Symptoms and Signs**—As chromophobe adenomata arise within the anterior lobe the early symptoms have to do with increased pressure within the sella turcica. Headache "behind the eyes," is thought to be a matter of tension upon the diaphragm of the sella. Later as the tumor expands, erosion of the diaphragm occurs and the tumor extends upward. The sudden disappearance of headache is considered to be due to rupture of the diaphragm with relief of the intrasellar tension.

As the tumor expands in the sella turcica the pituitary gland is greatly compressed with resulting functional deficiency. If this happens before

maturity has been reached all grades of defective development, as found in the craniopharyngiomata, may occur. Since the majority of the chromophobe adenomata develop in adult life, the symptoms then have to do with cessation of the gonadotropic function—menstrual in the female and impotence in the male. With the rupture of the diaphragm and extension upward of the tumor, pressure on the optic chiasm and hypothalamus occurs. Erosion of the bony walls of the sella turcica and of the clinoid processes tends to occur early and may progress to cause great destruction of the base of the skull.



Fig. 346.—X ray of lateral view of skull to indicate erosion of base from chromophobe adenoma in a male aged twenty.

**Treatment**—This is the commonest type of pituitary tumor in which surgical removal is attempted. Progressive loss of eyesight justifies surgical intervention. The results in skilled hands are highly satisfactory. X-ray treatment is of no avail in that the chromophobe cells are not radiosensitive. Replacement therapy for deficient pituitary function should be attempted with physiologically active preparations. This is more imperative in the growing child.

### Dwarfism

Pituitary dwarfism is a fairly well defined type of infantilism. Its onset is usually early in life but it is rarely recognized under five years of age. The functional disturbance is in the first instance a lack of growth, and later through deficiency of the gonad stimulating factor of the anterior pituitary, there is no sexual development. Cachexia does not occur. The indi-



individual reaches mature years with the physical development of a child. The body proportions are normal for the height, with the sexual organs in proportion. Secondary sexual characteristics are absent. Development of the reproductive organs in the female is arrested. The epiphyses remain open throughout life so slow growth may take place.

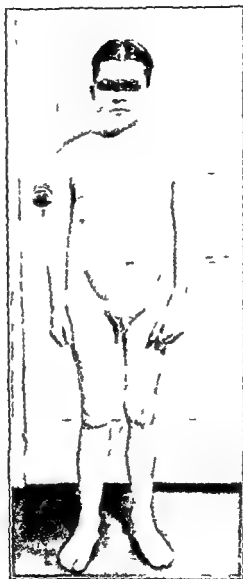


Fig. 34.—Hypopituitarism. Pituitary dwarfism. Aged twenty-one and height 4 feet 4 inches.

**Treatment**—Treatment of pituitary dwarfism should be based upon administration of the growth and the maturity factors of the anterior pituitary. These must, however, be given over a period of many years. Unfortunately many preparations of these factors are of low potency or effectiveness. Thyroid or thyrotropic extract may be helpful. Growth can be hoped for only so long as the epiphyses remain open and treatment should not be continued after their closure and sexual maturation.

maturity has been reached, all grades of defective development, as found in the craniopharyngiomata, may occur. Since the majority of the chromophobe adenomata develop in adult life, the symptoms then have to do with cessation of the gonadotropic function—menorrhoea in the female, and impotence in the male. With the rupture of the diaphragm and extension upward of the tumor, pressure on the optic chiasm and hypothalamus occurs. Erosion of the bony walls of the sella turcica and of the clinoid processes tends to occur early, and may progress to cause great destruction of the base of the skull.

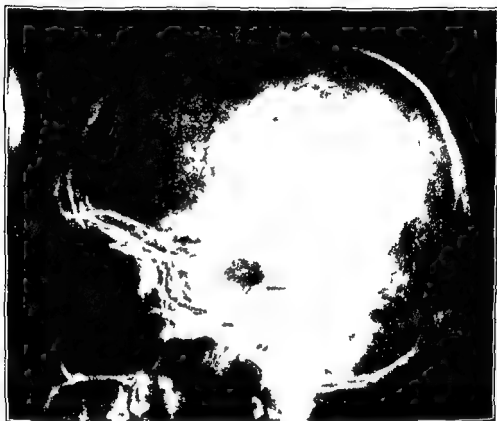


FIG. 346.—X ray of lateral view of skull showing extensive erosion of base from a chromophobe adenoma in a male aged twenty.

**Treatment**—This is the commonest type of pituitary tumor in which surgical removal is attempted. Progressive loss of eyesight justifies surgical intervention. The results in skilled hands are highly satisfactory. X-ray treatment is of no avail in that the chromophobe cells are not radiosensitive. Replacement therapy for deficient pituitary function should be attempted with physiologically active preparations. This is more imperative in the growing child.

### Dwarfism

Pituitary dwarfism is a fairly well defined type of infantilism. Its onset is usually early in life but it is rarely recognized under five years of age. The functional disturbance is in the first instance a lack of growth, and later through deficiency of the gonad stimulating factor of the anterior pituitary, there is no sexual development. Cachexia does not occur. The indi-

In the male the pituitary control of thyroid function is probably more uniform than in the female. Thus there is less danger of hypertrophy or involution deviating from the physiological range. This may explain the greatly increased incidence of all types of goiter in the female.

Due to the difficulty in coordinating the pathological histology with the clinical findings many clinicians have considered it wiser to employ a simplified classification. Recognizing these difficulties, the "thyroid group" at the Royal Victoria Hospital for many years has used a descriptive clinical classification which is similar to that recommended by the American Association for the Study of Goiter.

### Classification of Diseases of the Thyroid Gland

- A Goiter
  - 1 *Idolescent*—diffuse (colloid)
    - nodular (colloid)
  - 2 *Yontoxic* —diffuse (colloid)
    - nodular (colloid or adenoma)
  - 3 *Toxic*
    - Simple—diffuse (colloid type that becomes toxic)
      - nodular (cystic or adenoma)
    - Exophthalmic—diffuse (Graves' disease)
      - nodular (Graves' disease that has developed nodules in previous cycles of hyperplasia and involution)
- B Thyroiditis—acute
  - chronic
- C Tumors—benign
  - malignant

### Adolescent Goiter (Diffuse and Nodular)

**Definition**—Adolescent goiter is a diffuse or nodular enlargement of the thyroid gland occurring in growing children and usually having its onset at the time of puberty. This enlargement is due to an increased colloid storage resulting from iodine deficiency.

**Occurrence**—There is a world wide relationship between the incidence of adolescent goiter and the amount of iodine in the soil. Iodine poor soils will result in a deficient iodine content in the drinking water, the vegetables and other foodstuffs. On the North American continent the glacial age resulted in the surface soil being carried southward so that an extensive 'goiter belt' traverses the continent from east to west. This 'goiter belt' includes the St. Lawrence basin, the Great Lakes basin, the Upper Mississippi valley and the northwest states and provinces. In other parts of the world the incidence of adolescent goiter is high in mountainous districts, such as the Alps, the Peak Country of England, the Himalayas and the Pyrenees areas which have been denuded of their surface soil and are deficient in iodine.

## DISEASES OF THE THYROID GLAND

### Introduction

The thyroid gland is derived embryologically as a median invagination of the endoderm of the floor of the pharynx between the first and second pair of pharyngeal pouches. These cells grow downward and ultimately, at the level of the second and third tracheal rings, form two lateral lobes with a connecting isthmus. In the process of forming the lateral lobes, this sausage shaped tube coils upon itself endlessly like a bag of worms, which accounts for the characteristic picture upon cross section.

As understood today, the specific function of the thyroid gland is to manufacture the hormone thyroxin ( $C_{15}H_{11}O_4NI_4$ ) which is carried via the circulation to all nucleated cells of the body. For the formation of thyroxin, iodine is necessary, the gland using about 0.75 mg per day. The total tissue content of thyroxin is about 16 mg. With a total cessation of thyroid function the oxygen consumption or basal metabolic rate falls to minus 40 per cent. Thus each milligram of tissue thyroxin would account for about 2.5 per cent of the body's basal metabolism.

The thyroid gland is a very mobile organ undergoing a cyclic change in women from puberty to the menopause. These cycles are a matter of hypertrophy and involution occurring in relation to the menstrual periods. The hypertrophic phase is under the control of the anterior lobe of the pituitary through its thyrotropic factor, and occurs in the premenstrual period. Subsequently as the pituitary stimulation is released, involution follows. For the cycle to complete itself in a normal manner an iodine supply is essential. If lacking or defective, the gland becomes enlarged with increased colloid storage (an exaggerated involution). It has been thought that lack of iodine stimulates hypertrophy to progress into hyperplasia with increased blood supply and a depletion of the stored colloid but this is doubtful. What part the thyrotropic factor of the anterior pituitary plays in carrying hypertrophy into hyperplasia is not known. Experimentally the thyrotropic factor can produce hyperplasia with a raised basal metabolic rate, and if its administration is continued, an antithyrotropic factor develops which neutralizes the thyrotropic factor, with disappearance of the hyperplasia and the raised oxygen consumption. Whether in the toxic goiter there is a failure of antithyrotropic factor control is not known. After total thyroidectomy and in myxedema an increased amount of the thyrotropic factor circulates in the blood. In exophthalmic goiter no increase of the thyrotropic factor has been found in the urine.

Viewing the mobility of the thyroid in this light, the occurrence of colloid goiter is initiated by a lack of iodine which interferes with the normal cycle of hypertrophy and involution really a matter of excess involution. The nodular colloid goiters may result from involuntary cystic changes or a cystic involution following mild degrees of hyperplasia. The development of toxicity may be determined by the balance between thyrotropic and antithyrotropic factors which would limit the progress of hypertrophy into hyperplasia. This is a hypothesis only its verity will have to be proved in the future.

table salt should be used. The addition of iodine to the drinking water has been instituted without harm if the concentration is within reasonable limits. The excessive use of iodine both in salt and water is dangerous. Not only is it apt to produce iodine intoxication but it may cause signs of thyroid toxicity. School children spring and fall should receive 5 to 10 mg. of iodine twice a week. This can be administered as sodium iodide, hydroiodic acid, or in the form of a chocolate tablet (Iodocasein or Iodostarine).

**Curative**—The results of treatment of adolescent goiter once established have been exceedingly disappointing. This statement is based upon extensive experience at the Royal Victoria Hospital in Montreal. Iodine results in an increase in intracapsular tension due to increased colloid storage. The combination of iodine and thyroid where the basal metabolic rate is low has also given indifferent results. Iodine dosage should be small and given in interrupted periods. Possibly treatment has prevented some goiters from becoming larger. Over 90 per cent disappear spontaneously with maturity. Those having a nodular character are more liable to persist and develop into the nodular colloid goiters of middle age.

### Goiter—Nontoxic

**Diffuse**—This is a diffuse enlargement of the thyroid gland occurring in an adult, due to increased colloid storage. It may have followed an adolescent goiter. There are no signs of toxicity, and the only symptoms present are referable to pressure on the trachea. The basal metabolic rate is normal or slightly lowered.

Its incidence and etiology have the same basis as the colloid goiter of adolescence. In time as the gland passes through cyclic phases of hypertrophy and involution with a tendency to increase in size, cystic areas of degeneracy may appear producing elastic nodules. These are the colloid strumas so commonly seen among the adult population in goiter districts. Intrathoracic extension of these cystic nodules may occur.

Complications of the diffuse colloid goiter in the adult are only a mild degree of tracheal compression. Their removal is rarely justified due to the probability of a postoperative myxedema.

**Nodular**—Goiters of this type may be nodular from involutional cystic areas of degeneration or from adenomas. Most long standing diffuse colloid goiters in adults become nodular and as a rule it is only after their nodular character has developed that they cause pressure complications and require surgical removal.

Adenomas of the thyroid are usually unilateral but may be bilateral. They may be small or as large as a lemon. The very large nodular enlargements without toxicity always contain cystic areas of degeneration.

Thyroid adenomas are supposed to be of fetal origin and are capable of becoming toxic. Hemorrhages may occur into them, and a few develop malignant changes. Others undergo cystic degeneration.

**Pathogenesis**—(Adenomata) It is considered that the adult thyroid gland contains small nests of cells capable of regeneration into tumorlike

**Etiology**—As the etiology of all types of colloid goiter, both in the child or adult, is the same, it will be discussed at this time. There are two main schools of thought as to its cause, one upholds iodine deficiency, and the other an infectious agent. The incidence of colloid goiter is certainly greatest where there is a deficiency of iodine in the drinking water and foodstuffs, but McGarrison's studies in India indicate that pollution may be a contributing factor. On the North American continent the importance of a lack of iodine as an etiological factor has been amply demonstrated by Marine. The prophylactic use of iodine among the school children of the Great Lakes district has tremendously reduced the incidence of colloid goiter, a convincing argument. In Switzerland similar results have been obtained.

**Symptoms and Signs**—The enlargement of the thyroid gland develops gradually at the onset of puberty. It is usually diffuse but may be nodular and is always bilateral. When a colloid goiter especially of nodular type is found in younger children the mother frequently has myxedema. Most diffuse adolescent goiters, even if untreated disappear spontaneously with adult years. The nodular ones are more liable to persist. This increased colloid storage is definitely related to menstruation and becomes more marked at that time. In its early stages the diffuse enlargement of the thyroid causes no symptoms. The patient's attention may be called to it either by the school nurse or a friend. Later especially if the surface is nodular, mild symptoms of pressure on the trachea may be complained of.

Upon palpation the gland is usually soft but becomes more tense just before menstruation. If nodular there may be adenomata or involutonal cysts.

The basal metabolic rate is moderately lowered in about 50 per cent of these young people. It is common for it to range from minus 15 to minus 20 per cent. They present no definite symptoms or findings of myxedema. One should consider the condition a secondary hypothyroidism.

**Anatomical and Functional Pathology**—The enlargement of the thyroid gland is due to a distention of the acini with colloid which stains normally in microscopic sections. This distention may result in a flattening of the cuboidal cells lining the acini. The nodular character is usually a matter of an involutionary cycle which has followed a previous period of mild hyperplasia. Rarely circumscribed adenomata of fetal origin may be present. This colloid storage is viewed as a resting stage but again it would appear to be related to a deficiency in iodine available for the normal completion of the active secretion thyroxin. Since the thyroid is enclosed within a capsule the colloid storage would increase the intracapsular tension producing mild tracheal irritation and compression.

**Diagnosis**—The diagnosis of adolescent goiter is simply a matter of inspection and palpation. The enlargement is bilateral and nodules can be best palpated by lateral displacement of the trachea. A careful history and physical examination will exclude a toxic goiter. The basal metabolic rate is never raised but is usually slightly below the normal.

**Treatment—Prophylactic**—Preventive treatment of adolescent goiter is far more satisfactory than curative treatment. In all goiter districts iodized

of a recurrent laryngeal nerve produces a characteristic hoarseness of the voice until the other vocal cord compensates. Mediastinal obstruction may produce great venous stasis in the vessels of the neck and upper extremities through pressure upon the superior vena cava. Further, as the gland assumes a grossly nodular character the nodules may compress the remaining normal tissue leading to a certain degree of functional deficiency.

**Treatment**—In the case of involutionary nodules surgical removal is justified to relieve pressure. Following their removal the basal metabolic rate if it has been depressed, has been observed to rise appreciably, suggesting release of pressure upon potentially normal tissue. Small nodules, cystic or adenomatous, do no immediate harm. Potentially the adenomata are capable of developing an abnormal activity, or becoming carcinomatous. The onset of hyperthyroidism usually is insidious and material cardiac damage, even auricular fibrillation may develop before it is recognized. Therefore care must be taken to follow developments at regular intervals if removal is deferred. If the nodule is large enough to cause symptoms from pressure or pressure without symptoms, it should be removed. Until recent years many surgeons were content with unilateral operations with the result that five to ten years later the patient returned with a similar nodule in the other lobe. Careful examination at operation will usually reveal bilateral nodules which justify a bilateral thyroidectomy.

### Goiter—Toxic

Until recently a distinction was drawn between the nature of the toxicity in the nodular (toxic adenoma) type and that of classical exophthalmic goiter. It was suggested, based in part upon their response to iodine that the toxic adenoma of Plummer was a pure hyperthyroidism while the toxicity in exophthalmic goiter was due to some incompletely iodimized molecule or dysthyroidism. Later the response of both types to iodine was shown to be practically the same. Further the work of Rienhoff and others strongly points to the conception that both conditions result from the cycles of hypertrophy hyperplasia and involution.

**Simple—Diffuse**—Rarely does a diffuse colloid goiter become toxic without becoming nodular. The writer over a period of many years observation has seen one such case which followed excessive thyroid therapy in a young woman with a simple colloid goiter. After withdrawal of the thyroid medication the toxicity continued in a severe form with an increase of 40 per cent in the basal metabolic rate. A bilateral subtotal thyroidectomy was done. The sections of the removed tissue showed marked hyperplasia without stainable colloid. No eye signs developed.

**Simple—Nodular**—This is the toxic nodular goiter without exophthalmos. The typical picture has been well described by Plummer under the caption **Toxic Adenoma**. A nodular enlargement of the thyroid is present for five to fifteen years. An increase in the size of the nodule gradually or suddenly occurs. There develop at the same time nervousness, tremor, palpitation and loss of weight. The gland shows a moderately increased vascularity. The basal metabolic rate increases by 30 to 100 per cent. Myocardial changes and

nodules. The cells composing these nests may be fetal or fully differentiated in character. The nodular growths arising from the fetal cell nests are termed fetal adenomata, while those developing from the differentiated cells are termed simple adenomata. The factor that initiates this cell growth has been postulated as a lack of iodine. Adenomata arising from the mature cell show some attempt at capsule formation, while those developing from the fetal cells are usually multiple, have no colloid, and little supporting stroma. Cycles of hypertrophy and involution occur in these adenomata as in the rest of the thyroid tissue. Their cells are thus subject to hyperplasia and cystic degenerations. Necrosis of their central areas is not unusual.



FIG 248.—Photograph of a patient with nodular nontoxic goiter

**Symptoms**—(Adenomata) Usually a moderate enlargement of the thyroid has been present from five to ten years when a lump is observed to develop in one lobe. This nodule may increase in size slowly or rather rapidly. Palpation frequently shows the presence of multiple nodules. They are always movable, and may produce symptoms through pressure upon the trachea, recurrent laryngeal nerve, or esophagus.

**Complications**—If the nodular, cystic enlargement of the thyroid compresses or dislocates the trachea sufficiently, stridor may develop. Paralysis



of weight soon follows, due to the accelerated oxidation. The intake of food fails to supply the requirement, with the result that the balance is taken from the tissues. The patient is intolerant of heat. Diarrhea may occur periodically and seems to be due to an increased motor activity of the intestines.

Examination of the patient shows an anxious, jumpy, restless individual who is constantly occupied usually with little purpose. The expression is staring and the eyeballs appear shiny. A varying degree of exophthalmos is present which may be unilateral, but is usually bilateral. The skin is warm and



Fig. 49.—Photograph of a patient with exophthalmic goiter who periodically develops a mild degree of myxedema. Note exophthalmos and facial appearance.

moist which increases loss of heat by radiation, conduction and evaporation of water. In that way hyperthermia is avoided. The extended hands show a fine tremor, an important and constant finding in this condition. The pulse is rapid but regular and its rapidity is in proportion to the toxicity. This is one of the few conditions with tachycardia in which ventricular extrasystoles occur. The pulse pressure is high (80 to 100 mm. Hg) with a low diastolic pressure and a capillary pulse is usually present. The heart sounds are loud and slapping in character. Usually the thyroid gland is bilaterally enlarged, soft in consistency (if iodine has not been administered) and a throbbing pulsation can

sometimes auricular fibrillation may occur. In fact symptoms of circulatory failure may dominate the clinical picture and come on suddenly. Exophthalmos does not occur. "Toxic adenomata" respond well to iodine, and after being so prepared a bilateral subtotal thyroidectomy should be done. Recovery is excellent, and the tendency to regenerate is not so great as in exophthalmic goiter. Provided the heart has not been seriously damaged, the prognosis is good.

### Goiter—Exophthalmic, Diffuse and Nodular

#### Graves' Disease, Basedow's Disease

**Definition**—Exophthalmic goiter is a disease characterized by an accelerated state of tissue oxidation, and hyperactivity of the autonomic nervous system. The cause is unknown but seems to rest outside the thyroid gland.

**Etiology**—Studies upon the cause of exophthalmic goiter have not produced a satisfactory explanation. Many cases would seem to have a relationship to focal infection the tonsils being especially incriminated. Nervous shock or prolonged strain has preceded the onset of others. The idea that the sympathetic nervous system is in some way driving the gland to hyperplasia and hyperfunction has been suggested but no conception of the factor which initiates the stimulation has been offered. In exophthalmic goiter hyperadrenalemia is present in some cases but not invariably so. Its significance is not known. The idea that the toxicity is a dysthyroidism rather than a pure hyperthyroidism is losing favor. Experimentally in animals the complete picture, with the exception of the exophthalmos, has been produced by giving large amounts of thyroid extract or thyroxin. The factors determining the development of the exophthalmos are unknown.

With the later knowledge of the pituitary influence upon the thyroid through its thyrotropic factor a new conception is being formulated. This assumes that the thyrotropic factor is capable when unrestrained, of causing hyperplasia with hyperfunction. This conception is supported by certain facts: (1) experimental evidence that the thyrotropic factor can temporarily cause hyperplasia with a raised basal metabolic rate; (2) the high incidence of exophthalmic goiter in young women in whom one might expect to find instability of the cycle of hypertrophy and involution. This conception does not satisfactorily explain the disturbance of the autonomic nervous system other than as a secondary effect of the hyperthyroidism. The exophthalmos is not explained. Evidence that exophthalmic goiter is not a primary disease of the thyroid gland is the fact that thyroidectomy does not cure the disease. The basal metabolic rate may return to normal, and many symptoms disappear but nervous instability persists. Exophthalmos is frequently not influenced by thyroidectomy. The thyroid gland also shows a marked tendency to regenerate after its partial removal and the new tissue shows hyperplasia with hyperfunction.

**Symptoms and Signs**—The classical symptoms of exophthalmic goiter are nervousness, irritability, tremor and palpitation. These symptoms are referable to the state of hyperactivity of the sympathetic nervous system. The palpitation occurs at rest and is exaggerated by excitement and activity. Loss

of weight soon follows, due to the accelerated oxidation. The intake of food fails to supply the requirement, with the result that the balance is taken from the tissues. The patient is intolerant of heat. Diarrhea may occur periodically and seems to be due to an increased motor activity of the intestines.

Examination of the patient shows an anxious, jumpy, restless individual who is constantly occupied usually with little purpose. The expression is staring and the eyeballs appear shiny. A varying degree of exophthalmos is present, which may be unilateral but is usually bilateral. The skin is warm and



Fig. 349.—Photograph of patient with exophthalmic goiter who is intolerant of heat and developed a mild degree of myxedema. Note exophthalmos and facial appearance.

moist which increases loss of heat by radiation, conduction and evaporation of water. In that way hyperthermia is avoided. The extended hands show a fine tremor, an important and constant finding in this condition. The pulse is rapid but regular and its rapidity is in proportion to the toxicity. This is one of the few conditions with tachycardia in which ventricular extrasystoles occur. The pulse pressure is high (80 to 100 mm. Hg) with a low diastolic pressure, and a capillary pulse is usually present. The heart sounds are loud and slapping in character. Usually the thyroid gland is bilaterally enlarged, soft in consistency (if iodine has not been administered) and a throbbing pulsation can

be seen. Upon palpation the increased vascularity produces a thrill which can also be heard. Infrequently the thyroid is not enlarged in states of hyperthyroidism. In connection with the exophthalmos there are three signs of classical importance which are due to the anterior displacement of the eyeball. Stellwag's sign is the lack of winking. Moebius' sign is a weakness of convergence, and von Graefe's sign is the lag of the upper lids upon rotating the eyeballs from an extreme upward position downward.

The basal metabolic rate is raised in proportion to the degree of hyperthyroidism. Values of plus 25 to plus 50 per cent are found with moderate degrees of toxicity, while above 50 per cent the hyperthyroidism is severe. The blood cholesterol is lowered (normal 200 to 225 mg per cent) and varies inversely as the basal metabolism. Glycosuria, associated with hyperglycemia, is frequently present in the digestive periods. The fasting blood sugar is always normal but the glucose time curve may be identical with that of a mild diabetic due to delayed storage of glycogen in the liver. A fawn colored cutaneous pigmentation is not uncommon.

In the severe cases of exophthalmic goiter the pulse rate may become very rapid 140 to 160 per minute and the basal metabolic rate rise to 75 to 100 per cent above normal. Gastrointestinal crises and auricular fibrillation may occur. These 'crises' require active treatment, and may result in death from exhaustion or cardiac failure.

**Anatomical and Functional Pathology**—The thyroid gland is diffusely enlarged, soft and vascular. If iodine has been administered the gland may be firm and its surface slightly nodular from excessive colloid storage. Glands in long standing cases of toxicity are frequently nodular, due to involutional changes. If iodine has not been given the histological appearance is that of hyperactively functioning tissue. The acini are small and contain little stainable colloid. Their cells show marked hypertrophy with infoldings of hyperplasia in places filling the lumen. This hyperplasia may be patchy or diffuse. In addition there is an extensive small round cell infiltration. After iodine has been given the picture is that of a tissue trying to revert to the resting state. The acini assume more nearly their normal appearance and contain larger amounts of stainable colloid. Hyperplasia largely disappears although patchy areas may be found. The acinar cells become more cuboidal or compressed by colloid. The small round celled infiltration is not so marked.

The thymus is enlarged in more than 50 per cent of deaths from hyperthyroidism. The myocardium frequently shows degenerative changes and the muscles of the eyes fatty infiltration. In long standing cases of exophthalmos an increase of the retrobulbar fat is found. Diffuse lymphoid hyperplasia is present and the blood shows a relative and absolute lymphocytosis.

**Diagnosis**—The diagnosis of the fully developed case of exophthalmic goiter offers little difficulty. It is the incipient or concealed type that may be problematical. A careful analysis of the symptoms, the age and sex of the patient, the presence of an enlarged vascular thyroid and bilateral exophthalmos are important points. Rarely does the incipient case present more than a few of the symptoms and signs. A warm moist skin and slight tremor of the extended fingers should not be overlooked. There may be neither

exophthalmos nor a palpable thyroid gland. In hyperthyroidism the plasma cholesterol is lowered proportionately to the elevation of the metabolism. The fasting blood sugar is always normal but the digestion figure may be raised (120 to 200 mg per cent). A glucose time curve will suggest a mild diabetic state due to delayed storage of glycogen in the liver.

A raised basal metabolic rate that corresponds with the pulse rate at rest is the most important single laboratory finding. With the simplified means of measuring the basal metabolism (oxygen consumption) so generally used clinically care must be taken in the interpretation of the results. In the nervous apprehensive patient the first test is almost always too high. Most errors of technique (leakage etc.) tend to raise the oxygen consumption. Careful scrutiny of the character of the respiratory curve is of great help in differentiating the respiratory neuroses associated with anxiety states and hysteria from true hyperthyroidism. Respiratory irregularities of rate and depth are indicative of these (see Fig. 106 and 107). In doubtful cases repetition of the test will ultimately give comparable results. An increase in basal oxygen consumption may occur independently of hyperthyroidism as in leucemia with a pronounced leucocytosis rapidly growing neoplasms or numerous metastases where there is great cellular activity in fevers with an elevation of body temperature (one degree Fahrenheit raises it 7 per cent) in circulatory failure with dyspnea when it may be increased up to 20 per cent from the extra work required for respiration and in all conditions where there is increased muscle tone or gross tremors which cannot be controlled. When there is any doubt about the validity of the result it should be checked with the Douglas bag and gas analysis which will give a result less subject to the multiple errors of the ordinary oxygen consumption technique. The respiratory quotient (R.Q.) will be of aid in certifying to an accurate result.

Cases of early pulmonary tuberculosis may have nervousness tachycardia and loss of weight but their basal metabolism is normal when afebrile. Persons with respiratory neuroses offer the greatest test of diagnostic skill. The symptomatology is identical but the skin of the hands and feet is cold and clammy. The respiratory curve is irregular as to rate and depth (see Fig. 106). The true basal metabolic rate is normal. Cardiac decompensation without cause (rheumatic arteriosclerotic or syphilitic) should always be suspected as due to a latent hyperthyroidism. Similarly hypertension with a low diastolic pressure may be due to a similar cause.

It would seem obvious that in addition to the clinical factors in the recognition of disturbed thyroid function certain metabolic and biochemical tests are most helpful but under some conditions these do not give a specific answer as to presence and degree of thyroid toxicity. Recently such a specific answer has been much helped by two additional tests. The first of these is the estimation of the serum protein bound iodine. This is increased in proportion to the degree of true thyrotoxicosis and contrarily decreased in thyroid deficiency. The second test is through the use of radioactive iodine. When this is administered there is a greater uptake and retention in proportion to the degree of thyroid activity. It should however only be used in selected cases and under properly controlled laboratory conditions.

be seen. Upon palpation the increased vascularity produces a thrill which can also be heard. Infrequently the thyroid is not enlarged in states of hyperthyroidism. In connection with the exophthalmos there are three signs of classical importance which are due to the anterior displacement of the eyeball. Stellwag's sign is the lack of winking, Moebius' sign is a weakness of convergence and von Graefe's sign is the lag of the upper lids upon rotating the eyeballs from an extreme upward position downward.

The basal metabolic rate is raised in proportion to the degree of hyperthyroidism. Values of plus 25 to plus 50 per cent are found with moderate degrees of toxicity, while above 50 per cent the hyperthyroidism is severe. The blood cholesterol is lowered (normal 200 to 225 mg. per cent) and varies inversely as the basal metabolism. Glycosuria, associated with hyperglycemia, is frequently present in the digestive periods. The fasting blood sugar is always normal but the glucose time curve may be identical with that of a mild diabetic due to delayed storage of glycogen in the liver. A fawn colored cutaneous pigmentation is not uncommon.

In the severe cases of exophthalmic goiter the pulse rate may become very rapid, 140 to 160 per minute and the basal metabolic rate rise to 75 to 100 per cent above normal. Gastrointestinal crises and auricular fibrillation may occur. These "crises" require active treatment, and may result in death from exhaustion or cardiac failure.

**Anatomical and Functional Pathology**—The thyroid gland is diffusely enlarged, soft and vascular. If iodine has been administered the gland may be firm and its surface slightly nodular from excessive colloid storage. Glands in long standing cases of toxicity are frequently nodular, due to involutional changes. If iodine has not been given, the histological appearance is that of hyperactively functioning tissue. The acini are small and contain little stainable colloid. Their cells show marked hypertrophy with infoldings of hyperplasia in places filling the lumen. This hyperplasia may be patchy or diffuse. In addition there is an extensive small round cell infiltration. After iodine has been given the picture is that of a tissue trying to revert to the resting state. The acini assume more nearly their normal appearance and contain larger amounts of stainable colloid. Hyperplasia largely disappears although patchy areas may be found. The acinar cells become more cuboidal or compressed by colloid. The small round celled infiltration is not so marked.

The thymus is enlarged in more than 50 per cent of deaths from hyperthyroidism. The myocardium frequently shows degenerative changes and the muscles of the eyes fatty infiltration. In long standing cases of exophthalmos an increase of the retrobulbar fat is found. Diffuse lymphoid hyperplasia is present, and the blood shows a relative and absolute lymphocytosis.

**Diagnosis**—The diagnosis of the fully developed case of exophthalmic goiter offers little difficulty. It is the incipient or concealed type that may be problematical. A careful analysis of the symptoms, the age and sex of the patient, the presence of an enlarged vascular thyroid and bilateral exophthalmos are important points. Rarely does the incipient case present more than a few of the symptoms and signs. A warm moist skin and slight tremor of the extended fingers should not be overlooked. There may be neither

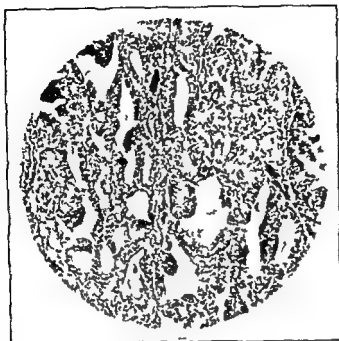


Fig. 350



Fig. 351

Fig. 350—Photograph of a micro section of thyroid gland from a case of exophthalmic goiter before the administration of iodine. ( $\times 130$ )

Fig. 351—Photograph of a micro section of thyroid gland from a case of exophthalmic goiter after the administration of iodine. ( $\times 130$ )

**Complications**—Foci of infection should be eliminated if possible, as they may increase the severity of the hyperthyroidism. Glycosuria is common during the digestive period. It must not be confused with true diabetes mellitus which may be found with exophthalmic goiter. Prolonged hyperthyroidism places a great strain upon the heart. Dilatation and auricular fibrillation occur but not as frequently as in the nodular toxic goiters which are undoubtedly of longer duration, and therefore the cardiac failure occurs in the more advanced age period, and is fraught with greater danger. Exophthalmos, if marked, is associated with edema of the conjunctivae, and inability to cover the cornea may allow physical trauma. Ulceration and rupture of the eyeball occur occasionally. Optic neuritis is a rare complication. At operation injury of the recurrent laryngeal nerve will cause a paresis or paralysis of a vocal cord with hoarseness. Such a paralysis may occur due to pressure of the goiter. Therefore a laryngeal examination should be carried out in all cases before operation, as a bilateral paralysis will cause alarming respiratory obstruction. Postoperative myxedema of varying severity may occur, or it may develop after the acute stage has disappeared spontaneously.

**Treatment**—The treatment of exophthalmic goiter requires in the first instance physical and mental rest. This can best be accomplished in a hospital away from the home and relations. Maintenance of nutrition is important. A high carbohydrate diet is well tolerated and helps to maintain the glycogen content of heart muscle and liver. Lactose up to 100 grams a day can be given in fluid drinks. On account of the raised metabolism, the total caloric requirement is twice that of the normal (3,000 to 4,000 calories per day). The calcium intake (milk) should be increased, since it has been shown that with hyperthyroidism a negative calcium balance occurs at the expense of the bone calcium. Water should be given freely. Sedative mixtures of phenobarbital or phenobarbital and sodium bromide help to bring quiet to the excitable nervous system.

**Medical Treatment**—Only the very mildest cases of exophthalmic goiter should be handled by prolonged medical treatment. Provided financial resources are adequate and time of little importance, prolonged bed rest and semi-invalidism may control the intensity of the symptoms until the disease runs its course. Throughout such periods the heart should be watched carefully to detect any dilatation or transient irregularity. The sympathetic depressant ergotamine tartrate (gynergen) has been used successfully. The dosage varies up to 10 mg per day by mouth.

**Surgical Treatment**—Subtotal thyroidectomy is a means of controlling exophthalmic goiter not a cure. To establish a cure in the full sense of the word it will be necessary to discover the primary cause and rectify it. There is no field of medicine where teamwork between physician and surgeon is of greater benefit than in the handling of a patient with a toxic goiter. Preliminary ligations and partial thyroidectomies are not necessary if certain precautions are observed. Iodine in any form should be administered only after a decision has been arrived at that an operation is advisable. If this precaution is taken and carried out the mortality from thyroidectomy will be lower. In hospital clinics the iodine fast patient is the dangerous and difficult one.



At the end of that period an attempt can be made to lower the toxicity by giving iodine again. The dosage will have to be larger to obtain a remission. Thyroidectomy should be performed after a moderate remission has occurred, as a pronounced one is not to be expected.

The technic of subtotal thyroidectomy is fully described in textbooks on surgery. There is, however, one point of extreme importance, namely, that it is better to remove too much thyroid tissue than too little.

**X ray Treatment**—The results of x ray treatment are no better than those from surgical treatment. X ray should be reserved for those cases refusing surgical intervention. In the case of regeneration after thyroidectomy x ray has a valuable place. The exophthalmic goiter that regenerates after a bilateral subtotal thyroidectomy will frequently regenerate after a second operation. By the use of x ray we have been able to control the toxicity as associated with the regenerated tissue, avoiding the possibility of multiple thyroidectomies.

**Thiourea Therapy**—In recent years, through the work of Astwood and his co-workers, another method of medical treatment has been evolved. This has been the use of thiourea and related compounds such as thiouracil, methyl thiouracil, etc. These latter have much less toxic properties than the former. They are considered to act through the reduction in formation of thyroxine. They can be used for two purposes. First if for any reason it seems unwise to prepare for operation with iodine and a longer period of rest and control is indicated, this can be accomplished by bed rest, symptomatic treatment, and the use of a thiouracil compound in dosages of 0.1 gm. four to six times a day. In seven to ten days indications of reduced thyroid toxicity will be evident and will be progressive with a return to normal in four to six weeks. Operation may now be indicated or second the drug may be continued in reduced amount of 0.1 to 0.2 gm. daily indefinitely. After six to eight months it may be stopped and in a considerable number of cases the remission may continue indefinitely with no more evidence of a relapse than is found after thyroidectomy.

The toxic effects of the newer compounds are comparatively rare and consist of fever, skin rashes, and severe granulocytopenia. Knowledge of their possible occurrence and close observation should render them of little danger.

Another possible advance in the medical treatment of thyrotoxicosis is the use of radioactive iodine. This however is at present in the realm of exploration and should await further knowledge and experience.

### Thyroiditis

**Acute thyroiditis** is an inflammation of the thyroid gland. It may be a simple productive swelling or a definite exudative process from invasion with pyogenic organisms. A primary bacterial infection of the thyroid is rare. More frequently it is secondary to a systemic or pyemic process. Tuberculosis of the thyroid is never primary.

The symptoms of an acute thyroiditis are painful swelling of the gland with increased heat and extreme tenderness. Usually it is bilateral. Moder-

to handle successfully. This state of over iodination results from prolonged iodine administration. A patient's first response to iodine is always the best.

**The Use of Iodine**—After the decision to do a thyroidectomy is reached iodine should be started in 5 minim doses, three times a day with meals. Lugol's solution (5 per cent iodine and 10 per cent potassium iodide) is most widely used. After about three days, the pulse will begin to be slower, and improvement in other symptoms follows with a falling basal metabolic rate. The maximum improvement is obtained in ten to twelve days, and thyroidectomy should be done at this time, or just before the period of maximum improvement, when the basal metabolic rate is dropping. This remission will last for a few days

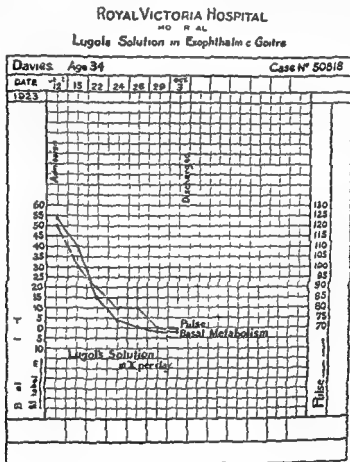


Chart XXX—The effect of Lugol's solution upon the basal metabolic rate in exophthalmic goitre

only, and subsequently the hyperthyroidism in all its features will gradually recur except that the weight may continue to increase. The cause of the remission is not known but Marine has suggested that the increased colloid storage increases intracapsular tension to a point where less blood flows through the thyroid gland with a lowering of the systemic toxicity. In time the circulation reestablishes itself at a higher level of intracapsular tension and toxicity recurs. If the patient has received iodine for an extended period of time and is iodine fast the thyroid will be tense frequently, slightly nodular, and signs of toxicity will be present. All iodine should be discontinued for one month and the patient kept in bed under the influence of sedatives

### Myxedema

**Definition**—Myxedema = a disease that develops in adults, due to a primary deficiency in function of the thyroid gland. The defective secretion of the gland results in a lowered thyroxin content of all nucleated cells with far reaching secondary manifestations. Myxedema may result from a primary atrophy of the gland, or secondary to a thyroidectomy or a thyroiditis.

**Etiology**—Spontaneous myxedema was first described by Gull in 1873. Up until recent years its prevalence was not appreciated. Mild forms frequently exist for many years without a correct diagnosis. The personal history will frequently not explain the cause of the atrophic thyroid state. The

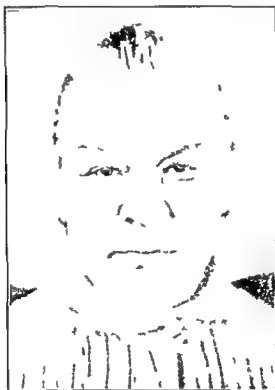


Fig 35.—Photograph of a case of myxedema. Note the thickness of the lips, puffiness about the scanty hair and the dull expression.

occurrence of the disease secondary to a subtotal thyroidectomy or a previous thyroiditis might be expected. In many nodular colloid goiters sufficient destruction or compression of thyroid tissue may cause myxedema. The toxic exophthalmic type of goiter that runs a prolonged course without surgical interference may gradually cure itself by fibrosis of the thyroid with sufficient destruction of glandular tissue as to permit myxedema. The incidence is five times greater in the female than in the male.

**Symptoms and Signs**—The symptoms of myxedema are extremely varied and their intensity parallels the lowering of the metabolic rate. The milder cases complain of fatigue, some dryness of the skin with rather frequent

ate compression of the trachea may develop. In acute purulent inflammations there is a conspicuous leucocytosis. Local applications of heat or cold usually relieve the symptoms, while purulent collections should be drained.

Milder forms of acute thyroiditis which sometimes occur with typhoid fever, pneumonia, etc., subside spontaneously. Extensive destruction of the thyroid tissue and resulting fibrosis lead to varying grades of myxedema.

**Chronic**—Chronic thyroiditis may follow an acute inflammation, and is characterized by a diffuse fibrosis. As this progresses the consistency of the gland becomes firmer, nodular, causing tracheal compression and sometimes involvement of one recurrent laryngeal nerve. In proportion to the destruction of the thyroid tissue so hypothyroidism even to myxedema follows.

Riedel's struma is a type of chronic thyroiditis which develops insidiously without known pre-existing thyroid disease. A progressive fibrosis of the gland takes place with pressure symptoms in the later stages. Its hardness may lead to the suspicion of carcinoma. The surface may be smooth or nodular, and it is usually fixed to the trachea and underlying structures. Operative interference is indicated only to relieve pressure as any extensive removal would be followed by myxedema.

### Tumors of the Thyroid Gland

**Benign**—Benign tumors of the thyroid gland other than adenoma are unusual. Infective granulomatous processes due to syphilis, actinomycosis and tuberculosis, occur rarely. Adenomas may develop degrees of hyperfunction with toxicity or progress into a true neoplasm. A sudden painful enlargement of an adenomatous nodule is due usually to hemorrhage.

**Malignant**—Carcinoma is the commonest malignant growth. Sarcoma occurs rarely. The *simplex* type of carcinoma is most frequently found and may cause early metastases without penetration of the capsule. The Mayo Clinic has stressed the etiologic relationship of the adenoma to carcinoma and on that basis recommends the removal of all adenomas.

The diagnosis of an early malignant tumor of the thyroid is difficult. It should be suspected in any thyroid enlargement especially if nodular, progressively increasing in size particularly if it is extremely firm or hard. With invasion of the capsule fixation to the underlying structures or attachment to the skin follows. Metastases take place early principally in the bones, lungs and liver. Cancer of the thyroid may cause a moderate increase in the basal metabolic rate and paralysis of the vocal cords.

Early operation in suspected malignant tumors is imperative. The hope of a cure is poor. X-ray or radium treatment should supplement surgical removal. Mention has been made above of the use of radioactive iodine in the treatment of thyrotoxicosis. The evidence available at present would indicate that it may have a greater use in the treatment of malignant thyroid tumors particularly when metastases have developed. The radioactivity is implanted in the thyroid tissues through their specific binding of the iodine. Much more careful work remains to be done as unexplained exceptions have been found particularly insofar as different metastases are concerned.

enlarged both to the right and the left. The x ray shows a ballooning of the ventricles but the cardiohepatic angle is acute. In many of these cases of apparent cardiac enlargement this is not due to the myocardium but to a pericardial effusion. The urine may show considerable albumin with or without granular and hyaline casts and there tends to be a hypercholesterolemia. The basal metabolic rate will range from minus 15 to minus 40 per cent. Altogether the picture is that of an individual mentally dulled and physically slowed up.

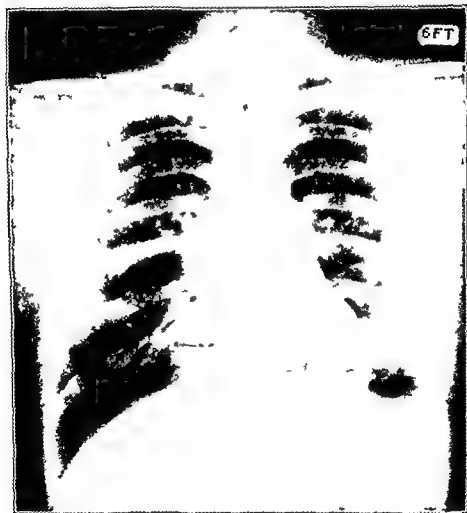


FIG. 364—X ray of the chest in the case of a patient after thyroid treatment showing a distinct reduction in the size of the heart.

**Anatomical and Functional Pathology**—The thyroid gland in primary myxedema shows atrophy of the acinar tissue and fibrosis with little round celled infiltration. When a colloid goiter is present the degenerative cysts through pressure destroy much of the functioning tissue.

The symptoms in the main are referable to the lowered metabolism which is due to the reduced thyroxin content of the tissue cells. The slow pulse and respiration, the mental dullness and physical lethargy reflect the sluggish

headaches or backaches. They may be sensitive to cold, given "to the hot water bottle," and desire extra blankets at night. As the basal metabolic rate falls lower (minus 30 to 40 per cent) a marked mental slowing takes place with forgetfulness, and slowness of speech. Unusual sleepiness and marked constipation may follow. Arthritic pains and muscular stiffness are common.

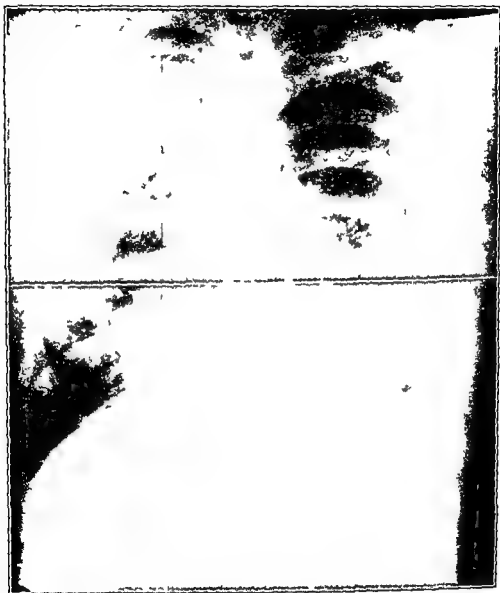


Fig 33—X ray of the chest in a case of myxedema showing the cardiac enlargement

Upon physical examination the appearance is important. The facial expression has lost its normal animation and become 'masklike' with a puffiness about the eyes and neck. Some pallor due to anemia is present. The skin is dry and may be scaly to a marked degree simulating ichthyosis. With this dry skin minor superficial infections are frequently present. There is usually a history of a gain in weight. The thickened puffy skin will not pit on pressure. There is bradycardia 50 to 60 per minute and the respirations may be slowed (8 to 12 per minute). The heart in severe cases is frequently

The iodine content of a thyroid preparation or extract is taken as the index of its biological activity. Although this is not exactly true it is the accepted standard. Different preparations, however, contain differing amounts of iodine. The following example will illustrate this. Burroughs Wellcome produce for use in Canada and Great Britain a thyroid extract which contains 0.3 gm per cent of iodine according to the B.P. requirement. But they produce for use in the United States a thyroid extract containing 0.2 gm per cent of iodine (0.17 to 0.23 gm) to meet the U.S.P. standards. Parke Davis also produces for use in Canada a thyroid extract containing 0.3 gm per cent of iodine to meet Canadian standards but this is known in the U.S.A. as

thyroid extract strong to distinguish it from the standard U.S.P. extract containing 0.2 gm per cent of iodine. It will therefore be seen that there are two official preparations of thyroid extract used on this continent which vary in strength by 50 per cent iodine content. This is most important in the treatment of myxedema. A careful record of the pulse rate must be kept and at biweekly intervals the basal metabolic rate should be taken. Precordial pain even of a mild degree is a warning that too much work is being thrown upon the heart. Proceed more slowly. It may take three months to bring a severe case back safely to the normal. The maintenance dose in most severe cases of myxedema is approximately gr 1 per day but each case must be treated individually according to their needs. A rigid standard for all cases cannot be laid down as the degree of thyroid deficiency is an individual variation and does not necessarily run parallel to the reduction in the basal metabolic rate. It is striking that cases of primary myxedema are much more sensitive to thyroid preparations than cases of secondary hypothyroidism. The latter may tolerate 10 to 20 gr ms of the same thyroid preparation with an unaltered pulse rate and little effect upon the basal metabolic rate. The explanation for this is not clear. There is little need for altering the maintenance dose after it is once established.

The use of thyroxin intravenously is dangerous. Once administered there is no way of neutralizing its action which may produce serious or even fatal cardiac effects.

### Cretinism

**Definition**—Cretinism is a disease referable to defective thyroid function which has its onset in fetal life or infancy. Secondly other ductless glands may become involved. The disturbance affects both the physical and mental development.

**Occurrence**—In the parts of the world where colloid goiter is endemic cretinism is not rare. Such areas are found in Switzerland, the Himalayas and in other regions where the soil is deficient in iodine. Cretinism of this type is spoken of as *endemic* while a *sporadic* type may develop in early life following some infectious fever. Such cases have no relationship to goiter districts.

**Etiology**—Endemic cretinism usually has its onset in fetal life the mother being deficient in thyroid function. This is closely related to the

tissue inactivity. Defective cutaneous circulation leads to the dry skin, inactivity of the sweat glands and susceptibility to infection. The skin changes, so characteristic of the disease, are not referable to the lowered metabolism alone. This would be suggested by their absence in secondary hypothyroidism and other states with a low metabolism.

**Diagnosis**—Myxedema is one of the diseases frequently undiagnosed in the early stages. Studies have shown that five to twenty years may pass from the onset of symptoms until proper treatment is started. The conditions with which it is frequently confused are chronic nephritis on account of the urinary findings, arthritis on account of the joint and muscle pains, myocarditis due to the cardiac enlargement and insufficiency, some types of anemia and neurasthenia. Since the introduction of the simplified oxygen consumption method for testing the basal metabolic rate, myxedema has been more frequently recognized in its early stages. If there is complete absence of thyroid function the basal metabolic rate is minus 40 per cent. One must not forget that there are normal people who have a basal metabolic rate as low as minus 15 per cent. An exact diagnosis depends upon the presence of the characteristic symptoms and signs associated with a lowered basal metabolic rate. Other conditions such as Addison's disease in which a greatly lowered metabolism may be found must be excluded.

**Complications**—Severe myxedema if present for many years leads to degenerative changes in many organs. The heart becomes greatly dilated and weakened. For a time it was thought that the enlargement was always referable to pericardial effusion. The electrocardiogram shows an inverted T wave in lead one with slurring of the QRS complexes. This with low voltage suggests the presence of a definite myocardial change. These are reversible reactions as when the metabolism is raised to normal, all this electrocardiographic evidence will disappear as the heart returns to its normal condition and size. The lowered metabolism is associated with hypercholesteremia which is closely associated with vascular sclerosis and hypertension. The chronic albuminuria may be due to anoxemia, and in time with the vascular changes may lead to chronic nephrosclerosis.

**Treatment**—The treatment of myxedema is highly gratifying. Its evolution is related to the history of the disease. Kocher recognized the myxedematous state following thyroidectomies and termed it *cachexia strumipriva*. Grafting of thyroid tissue was attempted, but the graft survived only temporarily. In 1891 Murray administered thyroid extract and obtained remarkable improvement.

Today thyroid gland extract or the active principle thyroxin is used exclusively in the treatment of myxedema. A remarkable mental and physical change occurs as the individual returns to the normal state. It is better therapy to change the level of metabolism gradually. At the low level the heart and other organs have been doing less work to maintain life. Any sudden elevation of metabolism may throw a sufficient strain upon the heart to cause precordial pain, dilatation and sudden death. There is more danger of heart failure when definite dilatation has been present before treatment.



per day. Why the cretin requires such large doses of thyroid is not clear. Adults with total myxedema require on an average only 1 gram of the extract for a maintenance dose.

Sporadic cretins theoretically should respond better to treatment. Unfortunately considerable delay occurs before the true condition is recognized. It seems probable that through delay in diagnosis in both endemic and sporadic cases irreparable damage has been effected to the more delicate and highly differentiated tissues.

### Developmental Anomalies

Since the thyroid is derived embryologically from an invagination and growth downward of the floor of the pharynx one would expect to find developmental anomalies arising from rests of the potential thyroid cells. The commonest of these are cysts which occur in the medial line from the root of the tongue to the inferior mediastinum. In the latter thyroid rests may develop into large functioning masses of cells which are termed substernal goiters. Lingual goiters have been observed located in the deep muscles of the tongue. These aberrant thyroid cells are capable of developing states of hyper- and hypofunction as in the unusually situated gland.

### Hypometabolism Without Myxedema

A lowered basal metabolic rate occurs in several diseases without any clinical signs or symptoms of myxedema. This should be termed *secondary hypothyroidism*. It is characteristically seen in adolescent goiter where the basal metabolic rate frequently ranges from minus 15 to minus 20 per cent. Figures of minus 25 per cent have been observed. The hypometabolism is due to a deficient production of thyroxin secondary to a defective iodine supply.

Low metabolisms are seen in diseases of deficient function of the pituitary, adrenal and gonad glands. No findings characteristic of myxedema are present. In the case of the pituitary and the gonads the normal controlling influence of these glands upon the thyroid would appear to be defective. The adrenal raises metabolism both through the effect of adrenalin upon the cells directly and through the stimulating effect of adrenalin upon the thyroid. With deficient adrenalin production the basal metabolic rate may fall to a very low figure again without myxedema. Levels of minus 48 per cent have been reported lower than is usual with total myxedema.

### The Thyroid and Pregnancy

At the time of pregnancy an increased call is made upon the thyroid function of the mother. This is reflected in a slight physiological fullness of the gland due to increased colloid storage. If this enlargement becomes excessive it is a sign that available iodine is lacking and storage of colloid is excessive. Pregnant women should be supplied with a normal iodine intake. This precaution should be carefully observed in endemic goiter districts. Mothers with mild and moderate degrees of myxedema should have the deficiency corrected throughout the whole period of pregnancy. In addition to

available iodine in the mother's body. Severely myxedematous women are usually sterile. Sporadic cretinism is really myxedema in a child. The onset takes place in infancy and leads to retardation of physical and mental development.

**Pathology**—Most endemic cretins are born with practically no functioning thyroid tissue. An autopsy may reveal a complete absence or a gland that is small, atrophic, or highly fibrous. Sporadic cretins possess a thyroid gland characteristic of the end stages of a chronic thyroiditis.

**Symptoms and Signs**—The evidence of cretinism is rarely found at birth. Within a few weeks a suspicion may be aroused by a thickening of the skin and a hoarseness of the cry. The tongue becomes enlarged, and the facial expression may become piglike with the eyes set far apart. At the end of

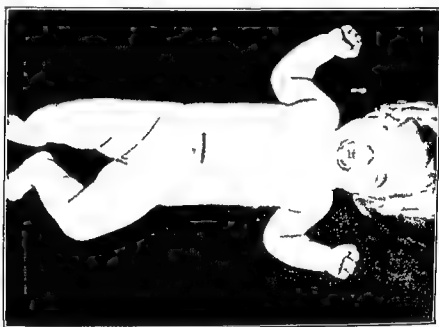


Fig. 3.—Photograph of a cretin aged twenty-three months showing characteristic large tongue, atonic muscular state and inability to stand. (Courtesy of Children's Memorial Hospital.)

one year delay in physical and mental development is evident. Dentition is slow and the teeth decay rapidly. There is a pot belly with prominent buttocks and scapular regions. In untreated cases these become increasingly evident as the months pass, and the child may be considered an idiot, although some are clownish and good natured, others seem to be almost like vegetables, sitting for hours in a state of seeming mental abstraction.

**Treatment**—Treatment of endemic cretinism is often unsatisfactory. The earlier the diagnosis is made the more hopeful is the outlook. Replacement therapy with thyroid gland or its extract is rational. Unfortunately the basal metabolic rate cannot be used as a guide to dosage but the clinical findings may be relied upon. Talbot suggests  $\frac{1}{2}$  grain of thyroid extract per day for infants from four to eight months of age, to be increased to 1 to 2 grains from one to two years and subsequently the dosage should vary from 3 to 6 grains.

carbohydrate metabolism ' more sensitive to the pituitary diabetic hormone (VTF) This however is a matter for further exploration

Whereas the functions of the medulla of the adrenals are comparatively simple in clinical medicine the influences or actions of the adrenal cortex are becoming increasingly diverse and to some extent complicated It is not within the province of this text to deal with all of the probable and indeed possible influences which extracts of the adrenal cortex may have not only on the special physiological processes but upon the structure and even architecture of the body as a whole In fact the time would seem to have arrived when many so called clinical syndromes must be viewed as ultimate complete anatomical or organismal breakdowns which are the unusual as compared to the partial deficiencies which in their modified form have a more diverse etiology based upon perverse physiological and psychological impulses

After the pituitary gland the adrenal in our present knowledge is the next most important But even so it is sometimes difficult to be certain as to whether the trains of physiological perversions are primarily situated in one or the other

Therefore it is necessary to find if possible some means or methods to differentiate these complex or at least interwoven functions or clinical patterns Although there are extracts of the cortical adrenal tissue which suggest or even demand attention in their role of therapeutic importance in unsolved systemic diseases the present discussion must be confined to our fairly well established fractions These are

- 1 The fraction which influences cation electrolytes and water balance or distribution in the body This effect is brought about by the action of the hormone on the reabsorption of these filtrates by the renal tubules If this hormone of the cortex should be absent or deficient sodium chloride and water are lost in the urine while potassium is retained in excess It is obvious from such an imbalance of control that there will be a serious sodium chloride depletion and dehydration with haemoconcentration and potassium intoxication

- 2 There has now been determined a cortical hormonal function which influences the carbohydrate protein and fat metabolism of the body in general It is well known that during periods of starvation the glycogen stores in the liver and muscles are replaced and maintained by the conversion of glucose and glycogen from body proteins This is apparently brought about by the action of an adrenal cortical hormone When this is deficient or absent this function may be impaired or indeed almost completely absent Therefore periods of relative hypoglycaemia may occur In fact the blood levels may be so reduced as to produce severe symptoms or even threaten life

- 3 In the classical description by Addison the presence of a brownish pigmentation of the skin and mucous membranes was one of the prominent features In fact today its presence is considered most important in the diagnosis of the complete syndrome and therefore has an important bearing upon the eventual prognosis The pigmentation is due to increased deposits of melanin The reason for this deposition is not known It cannot be attributed to any recognizable hormone fraction of the adrenal cortex But this is not surprising as the number of these fractions is being continually increased but in such manner

the thyroid gland or extract required, small daily doses of iodine are advisable. Such care of the expectant mother will materially reduce the incidence of thyroid deficient infants.

## DISEASES OF THE SUPRARENAL GLANDS

### Introduction

Although the suprarenal glands were known to exist in 1563 (Eustachius), no conception of their function was held until Thomas Addison, in 1855, described the clinical aspects of the disease which now bears his name. Shortly Vulpian, who discovered the chromaffin system, demonstrated the presence in the suprarenals of a substance which turned greenish on contact with ferric chloride (probably adrenalin). The vasoconstrictive action of medullary extracts was studied by Oliver and Schaefer and Talamone and Aldrich isolated the adrenalin base in crystalline form. In 1904 the chemical composition of adrenalin was determined by Jowett, and Stokes accomplished its synthesis. The function of the adrenal cortex was unknown until Rogoff and Stewart as well as Hartman prepared an aqueous extract with physiological action. Swingle and Pfaffner showed that the physiological action could be greatly enhanced by lipid extraction.

The suprarenal glands are two in number, one resting at the upper pole of each kidney in the retroperitoneal fat. They are composed of a cortex and a medulla. The cortex is made up of epithelial cells having their origin from the genital ridge. The medulla is composed of chromaffin cells arising from the embryonic sympathetic nervous system. The cortical cells have the same origin as the interstitial cells of the testis.

The exploration of the functions of the adrenal glands has expanded conspicuously in recent years. It is conceded that the medulla and the cortex have unrelated embryonic origins and as would be supposed essentially different functions.

The medullary cells have according to our present knowledge only one function namely the production of adrenalin (epinephrin). This has a strong vasoconstrictor effect on the peripheral arteries but has a dilating action on the coronary arteries and the bronchial musculature. As a consequence of general arteriolar vasoconstriction the systemic blood pressure is raised. If the therapeutic amounts administered are large there is consequent pallor due to vasoconstriction of the skin arterioles with palpitation of the heart. This however should be a relatively unusual occurrence but when spontaneous it is strongly suggestive of the presence of a pheochromangioma (see page 943).

The effect of adrenalin on the bronchial musculature is one of the most spectacular in clinical medicine. This is amply demonstrated in uncomplicated bronchial asthma where relief may be obtained in a matter of minutes.

Adrenalin has in addition certain other effects. It can produce hyperglycemia and glycosuria through release of glycogen from the liver. In this way it is an apparent antagonist to insulin. This is supposed to be effective through stimulation of the sympathetic nervous system. This might with justice be questioned and an alternative suggestion be offered that it renders

### Hypoadrenal Function

**The Exhaustion Syndrome (Hypoadrenalemia)**—The adrenal glands are capable of maintaining life in the presence of unusual strain or stress. Under conditions detrimental to life there is normally an hypertrophy of the glands. If this hypertrophy with increased function fails to occur a state of relative adrenal insufficiency may develop. This is termed the 'exhaustion syndrome' and is due to absolute or relative hypoadrenalemia.

**Symptoms**—The symptoms characterizing the syndrome are chronic fatigue, exhaustion, low blood pressure and in some cases a lowering of the plasma sodium with dehydration. The basal metabolic rate is usually normal or slightly depressed.

In doubtful cases evidence can be obtained by giving a low salt diet not more than one gram a day. If there is adrenal insufficiency this will cause a moderate blood concentration (hemoglobin elevated) and a negative sodium balance. In more severe cases a fall in the blood sodium and an increase in potassium will follow.

**Treatment**—Treatment consists in giving salt 10 to 15 grams per day, adrenal cortical extract and a liberal intake of water.

### Acute Insufficiency of the Adrenal Cortical Function (Waterhouse-Friderichsen Syndrome)

This occurs occasionally in severe infections with a bacteremia, particularly due to the staphylococcus or the meningococcus, a severe and precipitous collapse which closely simulates an Addisonian adrenal crisis. In these cases there is usually a hemorrhagic component. Such is not different from a similar state as classically described in many infectious diseases, hence the term 'black', 'scarlet fever', measles, smallpox, etc. But it is well known that the two infections mentioned above have proverbially associated hemorrhagic lesions and it is to be expected that the adrenal may share in this process. It is significant, however, that in the great majority of such cases coming to autopsy the lesion is bilateral.

There is another aspect of this syndrome which does not coincide with the above infections, namely its frequency in the causes of death in the newborn. As yet any definite connection between the above mentioned infections and its occurrence in these cases has not been established. But the fact remains that it should always be suspected when the clinical syndrome as described below occurs in cases with a severe bacteremia or in newborn infants.

**Symptoms and Signs**—As suggested above the outstanding features are the unexpected appearance of the symptoms and signs of profound shock with all the evidence of a complete adrenal insufficiency. Indicative of the severity of the process is hyperpnea. The occurrence of unexplained cyanosis, falling blood pressure, tachypnea, rapid and shallow breathing, mental confusion to semi or complete coma are not particularly unusual in overwhelming infections but to meet the criteria of this syndrome there must be presented some laboratory evidence of acute adrenal deficiency such as a definite hypoglycemia, a profound sodium and chloride loss, a conspicuous in-

mal amounts that experimental progress is handicapped, and furthermore, there are undoubtedly other fractions which remain to be recognized and amongst these is this elusive one which controls or at least determines the degree of melanin metabolism

4 The influence of the adrenal cortex upon genital development in both the male and the female is most intriguing. It is now well accepted that virilism and/or the so called Cushing's syndrome may be produced by hyperfunction of the adrenal cortex without demonstrable lesions of the pituitary gland. On the contrary evidence of hypofunction of the sex glands may also result from adrenal insufficiency as in the complete syndrome of Addison's disease.

It must not be conceived that disuse of the adrenals always leads to the complete clinical features of Addison's disease. As in diseases of other ductless glands there is often a quantitative modification of the whole function of the gland or any part thereof. This is emphatically emphasized in both the quantitative and qualitative physiological potency of cortical hormone preparations. Although this may be intriguing to the steroid chemist it is a perpetual source of ignorance to the clinician both in diagnosis and treatment. The chemical patterns of adrenal cortical function are just as quantitative as are those of the pituitary gland and it helps him but little at the moment to know that corticosterone with an oxygen atom at the  $C_3$ ,  $C_{11}$ ,  $C_6$  and  $C_{13}$  positions make it operative in regulating mineral and carbohydrate metabolism while removal of  $C_{11}$  oxygen atom increases sodium and chloride retention but bursts wide open carbohydrate metabolism while the addition of an oxygen atom at  $C_{11}$  (17 desoxycorticosterone) produces practically an opposite effect. But in time and with further critical clinical study these seemingly complex patterns will be elucidated and simplified both as to diagnosis and specific therapy.

Verzar has shown that in the adrenalectomized state there is a marked delay of absorption of glucose and fat from the intestinal tract. This delay is considered to be due to a failure of phosphorylation of glucose and fat in the intestinal mucosa. This failure of phosphorylation would appear to be due to the absence of cortin which is probably flavin phosphate and identical with vitamin B. In the absence of cortin adrenalectomized animals can be kept alive with flavin phosphite but not with holo flavin. This observation may be a fundamental one and if further investigated may throw some light upon the disturbed metabolism in cases of adrenal insufficiency. It may also lead to a clearer understanding of failure of fat absorption in other diseased states. (See page 639)

The suprarenal glands do not function independently of the other ductless glands. The anterior lobe of the pituitary gland secretes a hormone termed its adrenotropic factor which stimulates the cortex of the suprarenal. Removal of the pituitary results in atrophy of the suprarenal cortex. This is well shown in Simmonds' disease. Long has shown that complete adrenalectomy in a depancreatized animal will lessen the severity of the diabetic state and that if the animals do not eat they will die in hypoglycemia. In the main all substances injurious to the body tend to cause the adrenal to enlarge. J. C. M.

### Hyposuprarenal Function

**The Exhaustion Syndrome (Hypoadrenalemia)**—The adrenal glands are capable of maintaining life in the presence of unusual strain or stress. Under conditions detrimental to life there is normally an hypertrophy of the glands. If this hypertrophy with increased function fails to occur a state of relative adrenal insufficiency may develop. This is termed the exhaustion syndrome" and is due to absolute or relative hypoadrenalemia.

**Symptoms**—The symptoms characterizing the syndrome are chronic fatigue, exhaustion, low blood pressure and in some cases a lowering of the plasma sodium with dehydration. The basal metabolic rate is usually normal or slightly depressed.

In doubtful cases evidence can be obtained by giving a low salt diet, not more than one gram a day. If there is adrenal insufficiency this will cause a moderate blood concentration (hemoglobin elevated), and a negative sodium balance. In more severe cases a fall in the blood sodium and an increase in potassium will follow.

**Treatment**—Treatment consists in giving salt 10 to 15 grams per day adrenal cortical extract and a liberal intake of water.

### Acute Insufficiency of the Adrenal Cortical Function (Waterhouse Friderichsen Syndrome)

This occurs occasionally in severe infections with a bacteremia particularly due to the staphylococcus or the meningococcus a severe and precipitous collapse which closely simulates an Addisonian adrenal crisis. In these cases there is usually a hemorrhagic component. Such is not different from a similar state as classically described in many infectious diseases hence the term "black" scurlet fever marks smallpox etc. But it is well known that the two infections mentioned above have proverbially associated hemorrhagic lesions and it is to be expected that the adrenals may share in this process. It is significant however that in the great majority of such cases coming to autopsy the lesion is bilateral.

There is another aspect of this syndrome which does not coincide with the above infections, namely its frequency in the causes of death in the newborn. As yet any definite connection between the above mentioned infections and its occurrence in these cases has not been established. But the fact remains that it should always be suspected when the clinical syndrome as described below occurs in cases with a severe bacteremia or in newborn infants.

**Symptoms and Signs**—As suggested above the outstanding features are the unexpected appearance of the symptoms and signs of profound shock with all the evidence if sought of complete adrenal insufficiency. Indicative of the severity of the process is hypertension. The occurrence of unexplained cyanosis falling blood pressure tachycardia rapid and shallow breathing mental confusion to semi or complete coma are not particularly unusual in overwhelming infections but to meet the criteria of this syndrome there must be presented some laboratory evidence of acute adrenal deficiency such as a definite hypoglycemia a profound sodium and chloride loss a conspicuous in-

crease in the blood serum potassium, and clear evidence of pronounced hemoconcentration by the hematocrit. It is upon such evidence that a *factual diagnosis* may be made, which however, is only occasionally possible. On the other hand a speculative diagnosis of such can do no harm, and the therapy indicated, whether the diagnosis is specifically demonstrated or not, is in the way of wisdom.

**Treatment**—The treatment is a matter of common sense. The infection must be combated by all means in our power, by sulfonamides, penicillin streptomycin etc. One cannot tarry in determining the specific agent responsible. Time may reveal this. The hemoconcentration and dehydration must be combated by the infusion with plasma glucose and hypertonic sodium chloride solutions. This in its essence is acute substitution therapy and massive injections of aqueous adrenal cortical extracts of hopeful potency should be continued until the acute condition has been surmounted. Too much can seldom be given but it should never be held to be too little and too late. There is one word of caution however—excessive doses of desoxycorticosterone acetate may produce fatal results through producing cardiac distention and pulmonary edema by distic and acute increase of the blood volume.

There is still one aspect of this syndrome to be settled. If patients recover from this acute and almost catastrophic condition why do they not develop the classical syndrome of Addison's disease? This query is particularly directed to the supposed cases of recovery in the newborn.

### Addison's Disease

**Definition**—Addison's disease is a deficiency of the cortex and medulla of both adrenal glands.

**Etiology**—Older autopsy series show tuberculosis of the gland to be the primary cause in about 80 per cent of the cases. With recent studies and improvement in diagnosis atrophy and aplasias are now accounting for fully 50 per cent of the deaths tuberculosis comes second and syphilis third.

**Anatomical and Functional Pathology**—The anatomical lesions found at death in the adrenal glands are atrophy aplasia tuberculosis or syphilis. The atrophic gland is small (normal 4 to 10 grams) and characteristically shows a small round cell infiltration. The atrophy involves both cortex and medulla, and is bilateral. Small round cell infiltration takes place in other organs especially the liver. Aplasia may be bilateral or unilateral. If unilateral, the other gland may show marked atrophy. Tuberculosis when present is bilateral and causes extensive destruction of the gland by a fibrocaseous process. Necrosis may be small and patchy, but again the gland may be a necrotic mass enclosed in a fibrous capsule. The tuberculous lesions involve both medulla and cortex, and calcification as demonstrated by x ray is not unusual. The caseous masses are usually large weighing from 20 to 30 grams.

With atrophy or destruction of the adrenal glands a marked interference with their function follows. The cortical hormone controls the passage of sodium between the blood plasma and the tissue cell. If it is deficient the sodium tends to pass from the blood into the tissues. As it passes into the kidney cells it is lost to the body via the urine. Water follows sodium, with a



resulting dehydration and blood concentration. The failure of phosphorylation of glucose and fat in the intestinal mucosa with their impaired absorption has a causal relationship to the isthmus undernutrition and low glycogen reserve. There is also a low blood pressure, hypoglycemia and a lowered oxygen consumption. These may result directly through deficient cortical function or indirectly by this lack upon other organs.

**Symptoms and Signs**—The onset of the disease is usually insidious. Progressive weakness, asthenia and dizziness upon a change of posture are among the earlier symptoms. The cardiac shadow by x ray is small (see Fig 3a6) and resembles that remarked upon in pulmonary tuberculosis (see page 304). Pigmentation of the skin and mucous membranes due to melanin may occur early but is not necessarily present. As the disease progresses gastro-intestinal symptoms may be conspicuous. Nausea with irregular vomiting, diarrhea, and a gassy indigestion are prominent. In its later stages crises with collapse, severe dehydration, hypoglycemia and marked hypotension precede death.

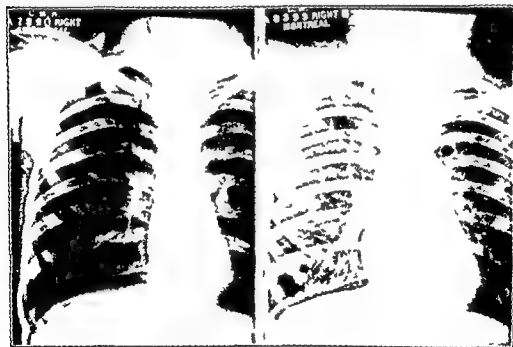


Fig 2 2

Fig 3

Fig 356—X ray of the chest of a case of Addison's disease in a crisis. Note the small and dropped heart.

Fig 3 7—X ray of the chest of the same case as in Fig 2a during treatment with sodium chloride. Note the change in the size of the heart.

Addison's disease offers a multiplicity of abnormal laboratory findings. The urine volume is decreased and concentrated, the urine contains creatin. The blood nonprotein nitrogen and urea are raised, a result of impaired renal function. The basal metabolic rate is usually low even to minus 48 per cent. Achlorhydria is present. The severer cases show a lowering of the blood sodium with evidence of blood concentration. In crises the blood volume is

crease in the blood serum potassium, and also evidence of pronounced hemoconcentration by the hematocrit. It is upon such evidence that a factual diagnosis may be made which however, is only occasionally possible. On the other hand a speculative diagnosis of such kind do no harm, and the therapy indicated whether the diagnosis is specifically demonstrated or not is in the way of wisdom.

**Treatment**—The treatment is a matter of common sense. The infection must be combated by all means in our power by sulfonamides, penicillin, streptomycin, etc. One cannot tarry in determining the specific agent responsible. Time may reveal this. The hemoconcentration and dehydration must be combated by the infusion with plasma, glucose and hypertonic sodium chloride solutions. This in its essence is acute substitution therapy and massive injections of aqueous adrenal cortical extracts of hopeful potency should be continued until the acute condition has been surmounted. Too much can seldom be given but it should never be held to be too little and too late. There is one word of caution however—excessive doses of desoxycorticosterone acetate may produce fatal results through producing cardiac distention and pulmonary edema, distention and acute increase of the blood volume.

There is still one aspect of this syndrome to be settled. If patients recover from this acute and almost catastrophic condition why do they not develop the classical syndrome of Addison's disease? This query is particularly directed to the supposed cases of recovery in the newborn.

### Addison's Disease

**Definition**—Addison's disease is a deficiency of the cortex and medulla of both adrenal glands.

**Etiology**—Older autopsy series show tuberculosis of the gland to be the primary cause in about 80 per cent of the cases. With recent studies and improvement in diagnosis atrophy and aplasias are now accounting for fully 50 per cent of the deaths, tuberculosis comes second and syphilis third.

**Anatomical and Functional Pathology**—The anatomical lesions found at death in the adrenal glands are atrophy, aplasia, tuberculosis or syphilis. The atrophic gland is small (normal 4 to 10 grams) and characteristically shows a small round cell infiltration. The atrophy involves both cortex and medulla and is bilateral. Small round cell infiltration takes place in other organs especially the liver. Aplasia may be bilateral or unilateral. If unilateral the other gland may show marked atrophy. Tuberculosis when present is bilateral and causes extensive destruction of the gland by a fibrocaseous process. Necrosis may be small and patchy but again the gland may be a necrotic mass enclosed in a fibrous capsule. The tuberculous lesions involve both medulla and cortex, and calcification as demonstrated by x ray is not unusual. The caseous masses are usually large weighing from 20 to 30 grams.

With atrophy or destruction of the adrenal glands a marked interference with their function follows. The cortical hormone controls the passage of sodium between the blood plasma and the tissue cell. If it is deficient the sodium tends to pass from the blood into the tissues. As it passes into the kidney cells it is lost to the body via the urine. Water follows sodium, with a

their excretion is below the normal level the less will be the probable adrenal cortical activity. It must however be borne in mind that pituitary deficiency may lead to a similar reduction of their excretion.

- (b) If the diagnosis is in doubt it may be directly clarified by the administration of the adrenotropic hormone of the pituitary. If the response is favorable it indicates that the adrenal cortex is active and that the primary deficiency is in the former gland.

## 2 Indirect Methods—

- (a) Patients with adrenocortical insufficiency are extremely sensitive to insulin. Therefore a cautiously administered and controlled test as to this may be carried out. But it must always be borne in mind that there are other conditions in which increased sensitivity to insulin may be present. These are chronic diffuse hepatic disease, adenoma of the islands of Langerhans and pituitary gland deficiency. A somewhat similar test may be effected by placing the patient on a low carbohydrate diet with an anticipation of an aggravation of symptoms.
- (b) The sensitivity of a patient to a low salt (sodium chloride) intake may also be used as an indirect diagnostic procedure. A somewhat analogous test is based upon the disturbed kidney function to maintain a proper water balance. The Kepler-Lower water test is based upon the abnormality. The patient voids at 10 P.M. and all urine is collected and measured to 7 A.M. If there is adrenocortical insufficiency there will be an excess water loss during this time which will be demonstrated by a retention of water if the patient be given an adequate amount (20 cc per kilo of body weight) rapidly by mouth. If any hourly amount of urine passed during the next four hours exceeds the night volume it indicates that there has not been an excessive water loss during the night and therefore Addison's disease may be excluded. If the contrary occurs this disease must be considered as possible.

These indirect tests are fraught with danger and should be undertaken only in the hospital where constant vigilance is possible as they may precipitate an Addisonian crisis. This particularly applies to the first three.

**Complications**—An infection however mild is a serious complication in Addison's disease. The body fails to react either by a rise in temperature or by leucocytosis. Unless the greatest care is taken to maintain the glycogen reserve the patient may die in hypoglycemia. This is most common during convalescence about eight to twelve days after the onset of the infection.

**Prognosis**—The prognosis is determined in part by the basic nature of the disturbance. Tuberculosis of the adrenals is always fatal. With specific treatment syphilis of the adrenals should improve. In Addison's disease due to atrophy of the glands life can be greatly extended by the use of a cortical extract and salt. In all types of Addison's disease cortical extract and salt will improve the general health of the patients provided they maintain an adequate caloric diet. Their future depends greatly upon the maintenance of a glycogen

greatly reduced. Death is often sudden, and is preceded by a precipitant fall in the blood sugar. Increase of the blood potassium is of great significance.

It will be apparent from the account of the adrenal hormones outlined above and the concept that all functions of these may not necessarily be equally deficient that the pattern of Addison's disease may vary in detail in different patients. Also it has been found that these variations may not always run true to type in recurrent exacerbations in the same case. In some cases the normal pigmentation may be much more prominent and persistent than in others. Also a profound impairment of the carbohydrate and protein metabolism may be the outstanding feature while at other times the electrolyte and water imbalance dominate the clinical picture. It is true that the latter two may be fairly consistent causes of the Addisonian crises in any given case, but this is not without exceptions and one should always be alert for these exceptions as their appreciation in successful therapy cannot be overemphasized.

It has been mentioned above how the different functions of the adrenals may be deficient both independently and collectively. Therefore it is important at any one time to determine which one or ones may be principally at fault. The abnormalities of pigmentation have no effect *per se* upon the well being or life of the patient but only serve as an indication of the possible primary disturbance. Likewise is the effect on the gonads. This may be inconvenient but does not menace life. Here again it may act as a signpost.

**Diagnosis**—The typical case of Addison's disease shows progressive weakness with hypotension and a small heart (see p. 556). Gastrointestinal intolerance and pigmentation of the skin and buccal mucosa are present. If these findings occur associated with tuberculosis in some organ, a strong suspicion of Addison's disease is justified.

The laboratory examinations that will support the diagnosis are a low serum sodium (310 or less mg. per cent), a lowered basal metabolism (minus 20 to minus 48 per cent), evidence of impaired renal function (nonprotein nitrogen and urea moderately raised), creatinuria, achlorhydria, oliguria, and a negative nitrogen balance. The blood sugar will be at the lower level of normal (70 to 80 mg. per cent). In crises the serum sodium will drop, dehydration become more marked as evidenced by concentration of the blood and hypoglycemia of a severe degree may occur. A biopsy of the pigmented area of the skin will show its increased melanin content and tuberculous cases sometimes have calcified adrenals as demonstrated by x ray.

Diseases that result in a dark pigmentation of the skin offer most chance for error in diagnosis. Metallic poisonings especially silver, might be confusing. Hemochromatosis pigmentation occurs with glycosuria and an enlarged liver. Sections of the skin show an excess hemosiderin. Tuberculous and other peritoneal lesions may also exhibit cutaneous and mucous membrane pigmentation, as may also hyperthyroidism, idiopathic steatorrhea and pellagra.

There are however certain direct and indirect methods available for the evaluation of the adrenocortical functions.

### 1. Direct Methods—

- (1) The urinary assays of the 17 ketosteroids and of corticoids may afford valuable information as to the cortical activity. The more

to control the symptoms. If the serum sodium can be successfully elevated by salt less cortical extract will be required. Also the present standardization of the cortical extract is being carried out upon adrenalectomized rats and dogs, with little account being taken of the serum sodium level of the animals. In the near future no doubt these refinements will be more rigid, and gross variations in potency eliminated. Ordinarily a dose of 2 to 4 cc a day (1 cc containing the physiologically active fraction from 40 grams of fresh adrenal gland) is required.



Fig. 4. Patient with Addison's disease. Note pigmentation of neck and face. Blood sodium 31 mg per cent.

The primary effect of the cortical extract is to raise the serum sodium by withdrawing it from the tissues including the kidney cells. This results in less sodium being lost in the urine. Sodium chloride administered in 10 to 20

reserve in the liver. Before the use of a cortical extract cases of Addison's disease died in dehydration with marked hypotension. The blood sugar was low but not sufficiently depressed to be dangerous. Since a physiologically active cortical extract has been available, and the importance of salt has been appreciated, death has occurred most frequently from hypoglycemia precipitated by infection. There has been no evidence of dehydration.

**Treatment**—The treatment of Addison's disease consists of three phases: (1) measures to improve the general health and to combat the development of infections, (2) the more specific treatment of the defective cortical and medullary functions, and (3) the treatment of the basic specific infections: tuberculosis or syphilis, if present.

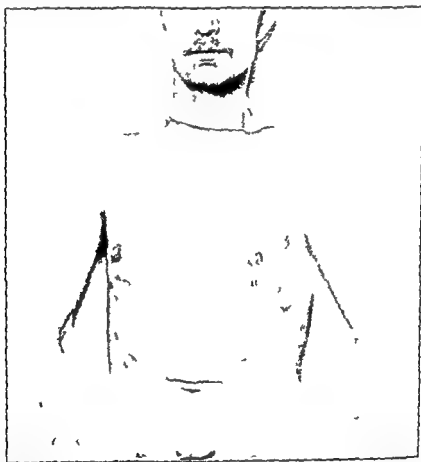


Fig. 358.—Photograph of a case of Addison's disease showing the diffuse pigmentation of the neck and body. At autopsy complete destruction of both suprarenal glands by tuberculosis was found.

The patient with Addison's disease is now a semi-invalid, so fresh air and sunlight should be encouraged. Avoidance of cold and no more than mild physical activity should be insisted upon. Systematic rest periods and a diet high in carbohydrate to maintain a good glycogen reserve are important. Several small frequent meals are best tolerated.

The adrenal insufficiency should be treated by a standardized cortical extract and salt. The dosage of the cortical extract will depend upon the level of the serum sodium. The lower it is, the more cortical extract is necessary.

to control the symptoms. If the serum sodium can be successfully elevated by salt less cortical extract will be required. Also the present standardization of the cortical extract is being carried out upon adrenalectomized rats and dogs, with little account being taken of the serum sodium level of the animals. In the near future no doubt these refinements will be more rigid and gross variations in potency eliminated. Ordinarily a dose of 2 to 4 c.c. a day (1 c.c. containing the physiologically active fraction from 40 grams of fresh adrenal gland) is required.



Fig. 29.—Photograph of woman, 38 year old, with Addison's disease. Note pigmentation of face, neck, hands and lower arms. B. I. 55; S. blood sodium 31.2 mg. per cent.

The primary effect of the cortical extract is to raise the serum sodium by withdrawing it from the tissues including the kidney cells. This results in less sodium being lost in the urine. Sodium chloride administered in 10 to 20

gram doses per day can be given in capsules of 0.5 gram each. This will help to raise the plasma sodium. A marked improvement in the well being of the patient will take place with such treatment. Weakness improves, hunger replaces nausea and vomiting, there may be a gain in weight with some decrease of pigmentation. The basal metabolic rate may rise, renal function improves, correcting the urea retention but a rise of blood pressure may not be outstanding. If hypotension is marked it may be improved slightly but does not return to a normal level. There is a conspicuous increase in the cardiac shadow by x-ray (see Fig 357). Wilder has found that the best results are obtained with a low potassium diet. Vitamin B<sub>2</sub> should also be given in full dosage. Desoxycorticosterone acetate has some of the physiological activities of cortin such as increasing blood pressure, reducing blood potassium, raising blood sodium etc. It does not affect the hypoglycemic crises. It may be administered intramuscularly or sterile tablets may be inserted into the muscles and produce an effect lasting for months. Sometimes the potassium may be reduced to levels dangerous to the nervous system. It is, therefore, most important that the requirements for desoxycorticosterone be carefully estimated before implantation as in addition to the low potassium effects on the nervous system the blood volume may be increased to a dangerous amount and acute cardiac failure may result. The same may occur with uncontrolled intramuscular injections.

In the urgency of collapse large doses of cortical extract, 10 to 20 cc (5 to 10 times the ordinary dose) should be given intravenously and repeated at four to six hour intervals if necessary. Hypertonic salt (5 per cent solution) and 10 per cent glucose in amounts of 200 to 300 cc intravenously should be beneficial. If the serum sodium can be maintained close to the normal level (normal 330 to 340 mg per cent) dehydration will correct itself. Until that can be accomplished fluids should be given freely and in crises intravenously. As soon as possible frequent oral electrolyte feedings should be given to help combat hypoglycemia.

Treatment of tuberculosis, if present, should be conducted along the lines recognized as suitable and syphilis if present, should be treated in a conservative manner.

### Hypersuprarenal Function

**Cortex**—Cortical tumors are associated with hyperfunction of the suprarenal cortex. These lesions will be described under Tumors.

**Medulla**—States of excessive adrenalin output occur. As Cannon has shown the emotions fear, anger etc. cause an increased adrenalin discharge which raises the blood sugar and makes energy rapidly available to meet the emergency. Mild repeated insults will cause an hypertrophy of the adrenal glands with excess adrenalin discharge. More severe insults if continued, will not result in adrenal hypertrophy and a degree of adrenal insufficiency may follow (exhaustion syndrome).

### Tumors

Tumors of the suprarenal gland may arise from both the cells of the cortex and those of the medulla. It will be remembered that the cells of the



cortex and the medulla have a different embryological origin and accordingly tumors arising from these cells would be expected to produce different results

### Tumors of the Cortex

Cortical tumors are composed of the epithelial cells characteristic of the cortex. Presumably the cells of the tumor have the same function as those of the normal gland. Thus we are dealing with a state of hyperfunction of the cortical cells. As yet no clinical entity has been described as being associated with an excess of hormone from a normal adrenal cortex.

According to the period in life at which this increased physiological action occurs, so different manifestations of the syndrome develop. In fetal life the cortical activity leads to congenital pseudohermaphroditism; in infancy to *pubertas precox*; and in adult life to virilism and hirsutism.

It may be convenient to classify these developments as follows:

- 1 Adrenogenital —
  - (a) Pseudohermaphroditism
  - (b) Pubertas precox
  - (c) Virilism
- 2 Adrenometabolic —
  - Cushing's syndrome
- 3 Mixed types

*Pseudohermaphroditism* may develop in both the male and the female but it is much commoner in the female. In the male there is the tendency to homosexuality. In the female the findings suggest a reversion to the male type: enlargement of the clitoris to the size of a small penis with failure of development of the uterus and ovaries.

*Precocious puberty* (*pubertas precox*) occurs before puberty and usually in a young child. It is more common in the male. It is characterized by an adult development of the secondary sexual characteristics as well as the sex organs themselves. The penis and testicles grow to adult size; the voice is low pitched; the pubic hair becomes abundant with the distribution of the adult male. In addition there may be excess growth of hair over the chest, back, arms and legs. *Pubertas precox* developing in the female child causes hypertrophy of the clitoris with excess growth of pubic hair, tending to revert to the male type in its distribution.

If the cortical tumor develops after mature development has taken place the findings are not so striking. There is a tendency both in the male and the female to become more masculine. This is usually described under the general term of *virilism*. The male may develop a greater growth of body hair of a coarse texture with a tendency for the skin to become thicker although cases have been reported of gynecomastia and feminism in the male. The female reverts to the male type: enlargement of the clitoris; atrophy of the breasts, uterus and ovaries; with the pubic hair of male distribution and a deep voice. A beard may develop and the skin become coarse.

Mention has been made on page 897 to the occurrence of Cushing's syndrome in lesions of the adrenal cortex. Many of the features described under

this heading have a similarity to those in the adrenogenital group. But there is one striking difference namely, the hyperglycemia which does not occur in the first group. This would indicate that the metabolic function of the adrenal was stimulated by some abnormal secretion. As this same syndrome may occur with a basophilic adenoma of the pituitary, certain thymomas and neuroblastomas, there is a strong suggestion that, although as mentioned above no definite clinical syndrome has been identified with an excessive production of normal adrenal cortical hormone, there may be other cortical fractions which are as yet unknown or at least unrecognized as being able to produce these clinical patterns.

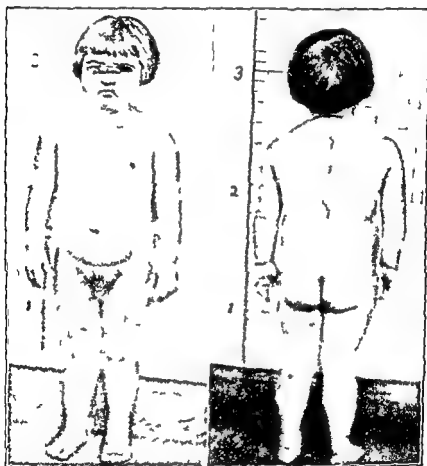


Fig 360

Fig 361

Fig 360—Front view of a female child aged four and a half years with adrenal cortex tumor. Note hirsutism and precocious puberty. (Courtesy of Dr Hector Mortimer.)

Fig 361—Back view of the same patient showing virilike arrangement of the hair on the back and overdevelopment of the shoulder girdle. (Courtesy of Dr Hector Mortimer.)

**Diagnosis**—The diagnosis of this condition is sometimes one of some difficulty for a number of reasons. The clinical pattern may be incomplete or there may be a mixed pattern with some of the features of the adrenogenital and the adrenometabolic groups. If a tumor is palpable in the loins or even if a tumor may be demonstrated by x-ray after percutaneous aspiration which should be carried out with the greatest caution and by experts and then is a last resort, the cause is fairly clear. It must be appreciated that these syndromes

may be associated with adrenal cortical hypertrophy alone without tumor formation. Furthermore somewhat similar syndromes have been found associated with tumors of the pituitary, thymus, ovaries and gonads but in the adrenocortical group the precocious puberty is not complete as menstruation does not occur in girls nor spermatogenesis or purpura in boys which is contrary to the precocity of pituitary and gonadal tumors. Endocrine assays may be helpful not so much in definitely pointing to the adrenal cortex as to lesions of other glands.

**Treatment**—The treatment of these cases depends upon the demonstrated presence of a tumor. If one is present its removal is indicated if metastases have not occurred. Some even advise exploratory operation in any case. Prior to our knowledge of the physiological action of the suprarenal cortex their removal was usually followed by collapse and death. However the literature contains an increasing number of cases where successful removal has been accomplished.

The cause of death following their removal is hypoglycemia. This is due to the fact that the other adrenal is usually atrophic. With the aid of an active cortical extract and salt the postoperative mortality should be much lower in the future.

### Tumors of the Medulla

There are three types of medullary tumors: neuroblastomata, ganglioneuromata and paragangliomata or pheochromocytomata. The neuroblastoma arises from the most embryonic type of cell and the paraganglioma from the mature chromaffin cell. The neuroblastomata have early metastases and run a malignant course. The paragangliomata are not so malignant and have been successfully removed.

### Paraganglioma

Of the medullary tumors the only one which produces a clinical pattern is the paraganglioma. It has been found almost equally in both sexes; it is more common on the right side but may be bilateral. As a rule they are small but they may attain sufficient size to be palpable or even to impinge upon neighboring organs. They usually are benign but a few cases have been reported which were malignant either systemically or locally invasive.

The clinical pattern of hyperfunction of the adrenal medulla caused by paraganglioma is that to be expected from an excessive dosage of adrenalin. It is as follows: (a) conspicuous hypertension (200 to 300 mm Hg), pallor, palpitation, precordial oppression and throbbing headache; (b) apprehension, blurring of vision, uncontrollable tremor, dilated pupils and hyperpnea; (c) hyperglycemia and glycosuria. As might be expected, all of these findings may vary from time to time in intensity. Further, although it is most distinctive for attacks to be paroxysmal, the hypertension and certain of the other symptoms and signs may be persistent and continuous and may lead to confusion in the diagnosis of essential hypertension. It should always be given consideration in the diagnosis of the latter. Some patients may associate the attacks with certain movements or articles of clothing such as a tight

girdle or belt bending to the right or left from the waist. This may be reproduced by deep palpation in one or the other or both loins. However the absence of these should not be exclusive.

**Diagnosis**—The diagnosis of paraneoplasia of the adrenal depends upon the recognition of the total syndrome over a period of time and the reproduction of attacks if possible. Percutaneous insufflation with x-ray examination is not advisable as the tumors are usually small and the dangers are excessive.

**Prognosis**—This rests upon two aspects. If the presence of such a tumor is not recognized there will develop in time all the vascular and organismal changes of structure and function associated with severe hypertension. The other important feature is the danger of collapse occurring during and after operation from acute adrenalin deficiency and the possibility of an associated acute adrenal cortical crisis.

**Treatment**—Removal of the tumor or tumors is likely to be a specific cure. It must be appreciated that these tumors may be multiple and further, that metastases may have occurred. If so, cure cannot be expected.

The patient should be carefully prepared for operation as if in expectation of an adrenal cortical crisis (see page 940). A sudden fall of blood pressure at operation or immediately following would probably indicate an acute adrenalin deficiency which could be countered by intravenous administration of adrenalin either by repeated injection or by the drip method (see page 1450). Adrenalin in oil intramuscularly is of value for its prolonged action in the days following operation. There should be constant vigilance to detect any evidence of cortical deficiency such as severe hypoglycemia rapid sodium and chloride loss, severe dehydration and persistent gastric disturbances. These should be treated as in an adrenal cortical crisis.

## DISEASES OF THE GONADS

### Introduction

It will have been apparent in the foregoing sections of this chapter that there is an intimate correlation between the functions of the different ductless glands. Each one may have what appears on first sight to be a primary purpose but yet when viewed from a broader angle they all conspire toward playing their part in preserving two biological fundamentals, namely self preservation and propagation. The primary purpose of the gonads is the latter, but they are influenced in this function by the others. It would be as impossible to consider the variable functions of the pituitary, suprarenal, thyroid, thymus and pineal glands without being impressed by their occasional and often spectacular influence on gonadal function as to view growth, nutrition, the strength to resist physical and environmental changes and the battle for the preservation of life without appreciating their dominating power to help preserve the species. All physiological processes are coordinated to make this preservation as certain as possible considering the vicissitudes to which the species is exposed. The intermingling of preservation and propagation are relatively indivisible although they may appear unconnected in a casual

survey. The race may not always be to the strong, but it undoubtedly is to the fecund, given proper environment. It has already been emphasized that although the endocrine organs have a profound influence upon the character and capacity of the body, they are also sensitive to gross abnormalities of the internal and external environment. The gonads are no exception to these influences. Therefore, in considering the diseases of the gonads it is necessary to take into account the function of the other endocrine glands, the quality and quantity of the diet and the presence of infections or chronic visceral diseases.

It may be stated with certainty that in addition to spermatogenesis and ovulation there are in the male and female secretions or hormones which determine the development of the secondary sex characteristics and in the female prepare the uterus for gestation. It is possible to have normal sex characteristics and sex organ development without normal fertility. The mysteries underlying propagation both in the male and the female are as much biochemical as anatomical and are only beginning to be understood. Such advances as have been made are viewed by the best and most conservative authorities as an earnest of the future. They are hesitant to be dogmatic or even slightly positive, but this has not prevented many whose knowledge of the fundamental and experimental difficulties is to say the least fragmentary, from postulating upon clinical problems with a certainty which is almost apocryphal. There are so many factors influencing sexual development and function that it is sometimes difficult to unravel the tangled skein. Under diseases of other ductless glands such as adrenal and pineal glands reference is made to their influence in producing abnormalities in sexual development. A sharp distinction must be appreciated between the development of these and an excessive libido. The latter is more dependent upon psychic stimulation than upon anatomical characteristics although unless these are fairly normal propagation may not be accomplished. It is true that there may be excessive sexual activity in the male and female without there being any demonstrable anatomical abnormality.

Before proceeding further it would be well to review briefly the important facts which are now fairly well known regarding the internal secretions of the gonads. For this purpose it seems reasonable to separate the male and the female secretions. In the period of childhood the progression is ordinarily without any spectacular developments but from the age of about eleven onward a differentiation between sexes occurs. This is so well known by the adult body and even appreciated by the children themselves that it would seem superfluous to recount it here. However for the matter of comparison this seems necessary.

**Puberty.**—The boy loses his baby fat, develops more muscle, hair begins to appear on the pubis, in the axillae, on the chest and chin, and eventually assumes the masculine distribution, the penis, scrotum, testicles, prostate, seminal vesicles and epididymis enlarge, and there is often a rapid skeletal growth with broadening of the shoulders, narrow pelvis and proportional lengthening of the long bones in relation to stature and a striking change in

girdle or belt, bending to the right or left from the waist. This may be reproduced by deep palpation in one or the other or both loins. However the absence of these should not be exclusive.

**Diagnosis**—The diagnosis of paraganglioma of the adrenal depends upon the recognition of the total syndrome over a period of time and the reproduction of attacks if possible. Percutaneous insufflation with x-ray examination is not advisable as the tumors are usually small and the dangers are excessive.

**Prognosis**—This rests upon two aspects. If the presence of such a tumor is not recognized there will develop in time all the vascular and organismal changes of structure and function associated with severe hypertension. The other important feature is the danger of collapse occurring during and after operation from acute adrenalin deficiency and the possibility of an associated acute adrenal cortical crisis.

**Treatment**—Removal of the tumor or tumors is likely to be a specific cure. It must be appreciated that these tumors may be multiple and further that metastases may have occurred. If so a cure cannot be expected.

The patient should be carefully prepared for operation as if in expectation of an adrenal cortical crisis (see page 940). A sudden fall of blood pressure at operation or immediately following would probably indicate an acute adrenalin deficiency which could be countered by intravenous administration of adrenalin either by repeated injection or by the drip method (see page 1450). Adrenalin in oil intramuscularly is of value for its prolonged action in the days following operation. There should be constant vigilance to detect any evidence of cortical deficiency such as severe hypoglycemia, rapid sodium and chloride loss, severe dehydration and persistent gastric disturbances. These should be treated as in an adrenal cortical crisis.

## DISEASES OF THE GONADS

### Introduction

It will have been apparent in the foregoing sections of this chapter that there is an intimate correlation between the functions of the different ductless glands. Each one may have what appears on first sight to be a primary purpose but yet when viewed from a broader angle they all conspire toward playing their part in preserving two biological fundamentals, namely self preservation and propagation. The primary purpose of the gonads is the latter, but they are influenced in this function by the others. It would be as impossible to consider the variable functions of the pituitary, suprarenal, thyroid, thymus and pineal glands without being impressed by their occasional and often spectacular influence on gonadal function as to view growth, nutrition, the strength to resist physical and environmental changes and the battle for the preservation of life without appreciating their dominating power to help preserve the species. All physiological processes are coordinated to make this preservation as certain as possible considering the vicissitudes to which the species is exposed. The intermingling of preservation and propagation are relatively indivisible although they may appear unconnected in a casual

period when the deficiency occurs. This is particularly evident in regard to the skeletal and sexual development cutaneous attributes, etc. These may be outlined as follows:

A. If it occurs before puberty one might expect:

(1) Anatomical features. At puberty the extremities continue to grow in comparison to the size of the trunk as the ossification centers are delayed in closing.

(2) The trunk as shown by the shoulders is narrow but the pelvis may be relatively broad simulating the female contour which may be accentuated by a certain degree of genu valgum.

(3) The voice remains childish due to arrest of laryngeal development.

(4) The secondary sex characteristics do not develop and this includes the absence of hair in the usual masculine distribution. In fact this usually remains juvenile with absence over the pubis and in the axillae with very scanty hair on the free chest, abdomen, arms and leg. It may resemble in this respect the most feminine of women.

(5) It would be expected that the genitals would remain childlike to outward appearances. Also the prostate does not develop nor do the testes and epididymides.

(6) Although there may be a certain degree of obesity as in Frohlich's syndrome this by no means necessarily occurs. Parallel to this there may be an apparent gynecomastia but this is not real and only occurs in those cases with obesity.

B. If hypogonadism is initiated after puberty the pattern is usually entirely different:

(1) The skeletal features do not occur and the patient to all intents and purposes remains as he is.

(2) The voice may lose some of its robustness and a bass singer may become a baritone or even a tenor.

(3) The secondary sex characteristics may become less masculine such as a decrease in beard, axillary and pubic hair and a reduction in muscular activity and stamina. But it is not to be expected that they lose ambition, intellectual drive and accomplishment. In fact many seem to divert their energies into quite productive avenues of endeavor. This however does not exclude the possibility of a psychoneurotic pattern due to a sense of inferiority and sexual frustration. Most probably this feature is analogous to the biological finality so often associated with the female menopause.

(4) The testes and prostate usually become smaller and the victim impotent but libido remains as this is a psychogenic function.

**Causes of Hypogonadism**—It must be appreciated that hypogonadism may be a matter of degree ranging from a slight deficiency to a complete loss of function. It is important to bear this in mind not only in the diagnosis but also in the prognosis and the expectations of successful therapy.

(1) *Primary Causes*—These rest in the testes themselves and may be congenital or developmental on the one hand or traumatic or infectious on the other. Primary congenital cases in which there is a testicular defect at birth

the voice due to alteration of the larynx. These are everyday occurrences and should not be belabored except in so far as they may not progress in a reasonably ordered manner.

In the female other distinctive changes occur in a normal fashion. The breasts develop, the nipples become more erectile, the pubic and axillary hair appear, the labia become more prominent and differentiated, the pelvis broadens and there is a rounded accumulation of panniculus over the pelvis, thighs, abdomen and shoulders, so well printed by the classical artists. The final culmination of this biological evolution is the appearance of the menses.

These pubertal changes in both sexes are brought about by an ordered interaction of internal secretions of the ductless glands which differ in the two sexes. The trigger mechanism which brings about these biological changes still remains a mystery, however. Under normal circumstances there would seem to be an evolutionary stimulus of unknown origin which primarily stimulates the pituitary gland or the sex organs to open the symphony. It would seem most probable that this originates in the pituitary.

It was stated in discussion of the pituitary that there were two gonadotropic hormones (namely I & II and L & II see page 891). The former influences the seminiferous tubules and the development of the follicles of the ovary and the latter the luteinization of the follicles and activates the interstitial cells of the testes. There may also be produced two gonadotropic secretions in the sex glands which counterbalance those of the pituitary. This, however, is still in the realm of speculation based on a modicum of suggestive evidence.

It would now seem proper to discuss separately the various abnormalities of the sexual development and function of the two sexes (J. C. M.)

### Abnormalities of the Male Gonads

- 1 Hypergonadism
- 2 Hypogonadism
  - (a) Primary hypogonadism (eunuchism)
  - (b) Secondary hypogonadism (eunuchoidism)
- 3 Male climacteric
- 4 Sterility

**1 Hypergonadism**—It is doubtful whether any clear syndrome of primary overactivity of the male gonads in either phase can be clearly recognized. Increase of libido which is a psychological phenomenon must not be confused with hypergonad activity.

Precocious sexual development has been found in overactivity of the pituitary, adrenal, thymus and pineal glands, but these cannot be considered as primary hypergonadism but rather an acceleration of the time factor in sexual evolution. A distinction must be drawn between anatomical development and functional activity. This is well illustrated in the life history of acromegaly.

**2 Hypogonadism**—The clinical features resulting from hypogonadism will be determined to a large extent according not to the cause but to the



Destruction of both testes by inflammations such as mumps or syphilis, bilateral destructive tumors or trauma (bilateral castration) is the other group of causes of primary hypogonadism and requires no further comment.

(2) *Secondary causes*—These rest outside the testes themselves and are chiefly represented by hypopituitarism or any hormonal or combination of hormonal defects which prevent descent of the testes.

**Diagnosis**—It has already been mentioned that hypogonadism is quantitative. To meet this variation it is customary to make a clinical distinction as to degree into eunuchism and eunuchoidism. The former designates complete absence of testicular function due to complete destruction of both testes, as mentioned above. The latter applies to a partial reduction in function which may be due to the primary causes such as undescended testicles and to the secondary causes.

The diagnosis might seem quite simple until one comes to analyze in detail the fundamental cause because upon this rests the success of treatment.

The anatomical diversions have the lead but they cannot provide the final answer in many cases as to the qualitative and quantitative functional disturbance. This may be obtained through a series of endocrine assays. This depends upon the assay of urinary testosterone which would indicate a quantitative activity of the interstitial cells of the testes. (On the other hand an assay of the I S H (see page 891) would give a lead as to the activity of the gonadotropic hormone of the anterior lobe of the pituitary. Another method of approach is a biopsy of the testicle. But in this there is always that chance fallacy of a minute piece of tissue not being representative of the whole. Finally there is the response to I H (see page 891) in the form of A P L and other trade names.

**Treatment**—It is obvious that in cases of undescended testicles a plastic operation might be of benefit. Though this is often wishful thinking it should be seriously but cautiously considered.

In all other cases there is the alternative of (1) stimulation therapy with gonadotropic hormones and (2) substitution therapy with male sex hormones.

It would be expected that in cases of eunuchism due to primary causes the former would be of little value as there would be nothing to stimulate. However in eunuchoidism due to such causes and in cases of undescended testicles stimulation therapy may produce good results. The use of A P L, the gonadotropic factor in human pregnancy urine also called chorionic gonadotropin, acts as a stimulus to the interstitial cells of the testis thus producing male sex hormone. It has been demonstrated that descent of the testis may be brought about by such means. It should however be used with caution in respect to where the testes are lodged. If they are within the abdominal cavity such treatment is apparently contraindicated. When all is said the treatment of these cases is still in a state of flux each one being treated independently or it may be said on an experimental basis.

On the other hand in eunuchism where there is complete absence of testicular function the problem is more direct. Where this condition develops after puberty one is faced with the decision as to whether the results are sufficiently inconvenient apart from impotence to warrant treatment. This is a

are rare. On the other hand hypogonadism due to mechanical interference with descent of the testes is relatively common. It has been demonstrated that the testes develop and function better in the scrotum than when they remain in the abdominal cavity, and there is a quantitative variation depending upon their position between these two sites.

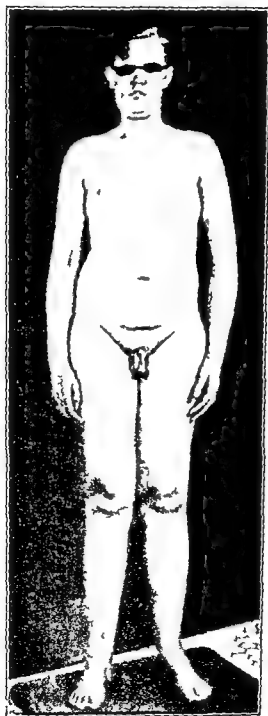


Fig. 36 --Photograph of a young man aged 17 at four. Height 5' 9", weight 111 pounds, basal metabolic rate -2.5%. A case of bilateral cryptorchidism and eunuchoidism. Note the undeveloped external genitalia, the delicate limbs, the narrow shoulders, broad hips and the lack of obesity.

In fact the question of sterility is a most complex problem. If it is to be analyzed seriously the man and wife should be referred after due explanation to a specialist in the subject as the problem requires a thorough exploration of both partners. In fact in the last analysis it is not a matter which should be within the diagnostic and therapeutic purview of the physician.

There is often a confusion in the interpretation of the terms *sterility* and *impotence* in the male. In the former there is not necessarily a lack of priapism although there is a deficiency of efficient spermato-genesis. In the latter there is usually an incapacity to copulate although by artificial methods it may be proved that spermatogenesis is normal. When cases of impotence are considered the normal decadence of sexual desire inherent in the advancing decades should not be included. Rather it should be restricted to those decades when normal sexual activity would be expected.

Impotence in the true definition of the term is a psychological reaction if organic neurogenic pituitary or local penile causes can be excluded. Therefore the indiscriminate use of stimulant or substitution therapy must be condemned unless it be a secondary adjunct to psychotherapy and then only in the hands of experts.

### Abnormalities of Female Gonads

#### 1 Hypergonadism

#### 2 Hypogonadism

(a) Primary hypogonadism (cauchism)

(b) Secondary hypogonadism

(c) Virilism

#### 3 Menstruation

#### 4 Sterility

1 **Hypergonadism**—A clear line of distinction must be drawn between hyperfunction of the gonads as represented by an exaggerated development of the primary and secondary sex characteristics and an increase of sexual desire. The latter is usually of psychic origin and may occur quite independently of the former. Its causes must be sought in the realm of local acquired organic genital or systemic lesions or through psychologic exploration.

(a) Primary precocious sexual development is due to ovarian tumors. These are either composed of granulosa cells or are of the order of teratomata. In the female when these lesions occur all the signs and symptoms of puberty may develop at an early age. These in no way differ from those to be expected in adult life.

(b) Secondary precocious sexual development is caused through suprarenal tumors. The characteristics have been described under *Pubertas Precox* in the section on Diseases of the Adrenal Glands and need not be repeated here.

(c) Hypergonadal function may develop as part of a general overdevelopment. This is commonly found to be a part of pituitary hyperfunction as seen in acromegaly. It is but part of this general condition and shares in its manifestations with other organs and systems (see page 89.)

personal question which has to be decided individually. That procreative powers can be revived is a vain hope that has been put forward by some of our charlatanish colleagues.

When probable eunuchism is manifest before puberty substitution therapy is indicated in the hope that this skeletal and epidermal state may be at least mitigated. This is best accomplished by the use of testosterone propionate in doses of 25 mg three to seven times a week parenterally. Methyl testosterone has been advocated by mouth but this is best employed as an alternate or for sustaining therapy. Implantation of pellets intramuscularly is advocated for desoxycorticosterone (see page 940) and the parenteral injection of testosterone propionate in oil have also been used. But after all, these methods are still in the experimental stage particularly as the maintenance dose has not yet been determined for such variable states between quantitative eunuchoidism and eunuchism.

**3 Male Climacteric**—In recent years much attention has been directed by some endocrinologists and psychiatrists to what they are pleased to call the male climacteric. It seems obvious that they do not mean the slow but progressive depreciation of spermatogenesis which may occur without any decrease in libido but rather a loss of libido with vague vasomotor and emotional instability which is common talk between women of a certain age of biological insecurity whether the conversation be at a tea party, a cocktail assembly, the dinner table or in the privacy of the connubial bed. In the opinion of the author it is doubtful whether there is enough evidence even to suggest such a physiological state in the male. It seems much more probable that this is purely a psychogenic state. There seems to be an irresistible desire on the part of many practitioners and even so called specialists to treat these cases with stimulation androgen therapy. It must be appreciated however that this state in many cases rests on a psychological or emotional basis. Therefore unless it be proved that spermatogenesis has ceased the employment of this therapy is strictly contraindicated. The reason for this is that if there be even a modicum of spermatogenesis let alone a normal amount this will gradually decline under this artificial stimulation (see below under sterility).

**4 Sterility**—Sterility in the male means but one thing namely the inability to propagate due to a quantitative or qualitative reduction of spermatozoa in the ejaculation. This may be brought about quantitatively by some obstruction in the seminiferous tubules, the prostate or even the urethra. This is therefore a problem for the urologist but it must be so determined by appropriate methods of examination.

On the other hand when such anatomical conditions are excluded it may be found that the sperm may be deficient in numbers or deficient in quality. This is therefore a primary defect in spermatogenesis. The causes for such are manifold. They range from a primary (congenital or required) anatomical lesion in the testicle, a deep emotional crisis which for some known or unknown reason has affected the spermatogenesis (see Chapter XVI) or is the result of other endocrine deficiencies particularly inherent in the pituitary and less so in the adrenal (J. C. M.)

In fact the question of sterility is a most complex problem. If it is to be analyzed seriously the man and wife should be referred after due explanation to a specialist in the subject as the problem requires a thorough exploration of both partners. In fact in the first analysis it is not a matter which should be within the diagnostic and therapeutic purview of the physician.

There is often a confusion in the interpretation of the terms *sterility* and *impotence* in the male. In the former there is not necessarily a lack of virility although there is a deficiency of efficient spermato-genesis. In the latter there is usually an incapacity to copulate although by artificial methods it may be proved that spermato-genesis is normal. When cases of impotence are considered the normal decreasence of sexual desire inherent in the advancing decades should not be included. Rather it should be restricted to those decades when normal sexual activity would be expected.

Impotence in the true definition of the term is a psychological reversion if organic neurogenic pituitary or local penile causes can be excluded. Therefore the indiscriminate use of stimulant or substitution therapy must be condemned unless it be a secondary adjunct to psychotherapy and then only in the hands of experts.

### Abnormalities of Female Gonads

- 1 Hypergonadism
- 2 Hypogonadism
  - (a) Primary hypogonadism (caenochism)
  - (b) Secondary hypogonadism
  - (c) Virilism

#### 3 Menstruation

#### 4 Sterility

1 **Hypergonadism**—A clear line of distinction must be drawn between hyperfunction of the gonads as represented by an exaggerated development of the primary and secondary sex characteristics and an increase of sexual desire. The latter is usually of psychic origin and may occur quite independently of the former. Its causes must be sought in the realm of local required organic genital or systemic lesions or through psychological exploration.

(a) Primary precocious sexual development is due to ovarian tumors. These are either composed of granulosa cells or are of the order of teratomata. In the female when these lesions occur all the signs and symptoms of puberty may develop at an early age. These in no way differ from those to be expected in adult life.

(b) Secondary precocious sexual development is caused through suprarenal tumors. The characteristics have been described under *Pubertas Precox* in the section on Diseases of the Adrenal Glands and need not be repeated here.

(c) Hypergonadal function may develop as part of a general overdevelopment. This is commonly found to be a part of pituitary hyperfunction as seen in acromegaly. It is but part of this general condition and shares in its manifestations with other organs and systems (see page 895).

(d) The syndrome of obesity and overdevelopment is characterized by the onset of a rather rapid growth in height and increase in weight about the age of nine or ten years. It has been seen more commonly in females. These patients are taller than the standard for their age. They are obese, they show premature closure of the long bone epiphysis. The onset of sexual maturity may be only slightly premature, but the development of the secondary sex organs



Fig. 63

Fig. 63—Photograph of a girl fifteen years of age, sexual development beginning at the age of nine.

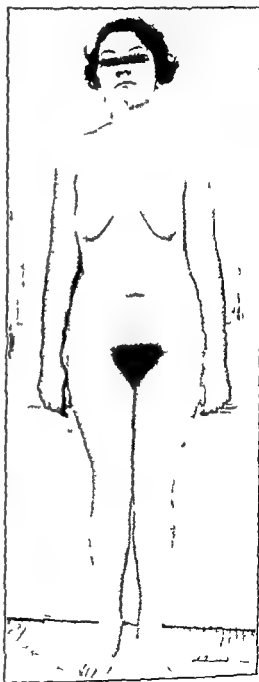


Fig. 364

Fig. 364—Photograph of the same patient as in Fig. 63, showing the effect of roid extract.

(Fig. 364) The general and permanent effect of the roid extract on the patient shown in Fig. 363.

and characteristics after the onset is very rapid and these girls have the appearance of mature women. The mental status is usually normal but they may show a prematurity in their mental attitude. This condition should be distinguished from Frohlich's syndrome the only common feature of the two being the obesity.

The diagnosis of these conditions gives little trouble as they are usually self evident to the observer. The syndrome of obesity and overdevelopment does not lead to any real abnormality and is chiefly of importance where age groups are likely to be treated alike without due allowance being made for individual variations in sexual and mental development.

The treatment of the primary group is removal of the ovarian tumor. The secondary group has been dealt with elsewhere.

## 2 Hypogonadism —

### (a) Primary hypogonadism

Total hypofunction of the gonads in the female before puberty results in female eunuchism. There is the expected abnormal growth of the long bones scanty hair growth on the mons and in the axillae and subcutaneous fat does not accumulate to form the rounded contour of the typical female figure. The buttocks and thighs are flat the breasts mannish and menstruation does not occur. There is no sexual desire and the social sense is lacking. The pelvic organs remain small and the vagina and labia remain undeveloped.

The diagnosis as a rule is not made until after puberty has been long delayed and the parents or the patient herself become worried about her lack of maturity. It has usually to be differentiated from other causes of amenorrhea and a complete examination in the nude to ascertain the absence of proper physical female development is imperative. A hasty diagnosis should not be arrived at as delayed pubescence is comparatively common. Lesions in the other ductless glands as well as organic diseases and intoxications must not be overlooked. (See below.)

The treatment at present is largely experimental and every case should be considered as an individual problem. All factors which may possibly in any way have a bearing on ovarian function must be thoroughly analyzed by biochemical methods and such treatment as may be indicated should be given a trial.

(b) Total hypofunction of the gonads in the female after puberty is perhaps best represented by the menopause. This however is often a gradual evolution that may take months or years before the complete clinical picture is produced. More striking examples are found in women who have been subject to a bilateral oophorectomy or have received intensive deep x-ray therapy with total destruction of ovarian function (see below.)

(c) Virilism should be restricted to women in whom masculine characteristics appear after a normal feminine development has occurred. It is usually associated with cortical tumors of the suprarenal glands. The skin becomes coarse and greasy. There is hirsutism with a masculine distribution of the pubic hair and a mustache and beard are usual. The clitoris enlarges and the labia uterus ovaries and breasts atrophy while the voice becomes deep and harsh and there is a reversal of sex interest.

**3 Menstruation**—The appearance of the menstrual flow has been a matter of wonder superstition taboo and religious and hygienic regulation since the earliest record of history. There is much evidence to indicate that it was considered by many races and religions to have a significant relation to ovulation or from a more practical point of view, to procreation. This was entirely the result of practical experience or what might be called empiricism. But it is interesting to note the periods of social seclusion or sexual abstinence which were enjoined after the menstrual period. Indeed our knowledge of the manner of the menstrual cycle was one of comparative ignorance up to the past decade or so. The means both surgical and medical employed to correct any of its abnormalities of timing or degree is ample evidence of this. In fact it may take another decade or so before some of these methods are discarded and replaced by a more rational therapy based upon known endocrinological concepts. It is not to be inferred from this that all is known about menstruation, but evidence is accumulating rapidly to clarify the problem.

In common with all biological cycles it is well to start at some point in order that the sequence of events may be followed with eventual return to the starting point. But before this is undertaken, it must be appreciated that the full psychosexual development is under the stimulus of the anterior lobe of the pituitary gland. This not only initiates but continues to control or perpetuate the sexual activity during the procreative life of the female.

The time comes when through this stimulus an ovum matures and breaks away from the ovary into the vast void of the peritoneal cavity but without it is directed to the fingered funnel of the Fallopian tube (right or left or both). Coincident with the normal development of the ovum and its release there is from the follicular cells of its origin secreted estrogen. The purpose of this secretion is to cause growth of the endometrial mucosa and exuberance of the vaginal epithelium to facilitate coitus. But as the follicle closes the type of cells changes from a follicular to a thecal character which forms the corpus luteum. Not only does then form change but also their function. The corpus luteum soon begins to secrete progesterone which in its name would imply still further acts to prepare the uterine mucosa by further growth to receive the fertilized ovum. If however this does not occur the exuberant uterine mucosa breaks down and is extruded in the form of menses which consist of nonclotting blood and fragmented mucosal debris. On completion there is left the basal layer of endometrium which during successive days rebuilds the mucosa in preparation for the succeeding cycle.

There are now several points which must be considered.

1 Ovulation is as a rule symptomless in other words it is a seemingly unconscious process. In certain cases however it is accompanied by painful sensations called *Mittelschmerz*.

2 It is important when investigating the cause of sterility between two partners to determine whether ovulation really does occur. A fair index of this may be revealed by a rise of body temperature at the time of ovulation. This is ascertained by recording the rectal or vaginal temperature each morning after sleep but before rising. An elevation of the body temperature to  $99^{\circ}$  to  $100^{\circ}$  F., or more at this time is compared to the so called normal is



strongly significant of ovulation. It must however be controlled with the temperature in the uterine menstrual cycle so that other causes may be eliminated.

Ovulation having occurred there is initiated a series of events which are almost perfect in their sequence. When the ovum has been released the site closes and the cells remaining change from follicular to luteal which form the corpus luteum. These cells take on a new although temporary function to secrete progesterone which accelerates and recelerates the growth of the endometrial mucosa to await the arrival of the impregnated ovum if and when this occurs. So the house is ready for habitation. If however nidation is not accomplished the prepared endothelium breaks down and is discharged in the form of menses. Then now occurs a period of relative biological quiescence until the next ovum matures and is discharged. This is commonly called the safe period when impregnation is reduced to a minimal hazard. But this is dependent upon a regular cycle of events which like all such have their exceptions.

### Disturbances of Menstruation —

**Menorrhoea** — Menstruation may never be established. If this be associated with dwarfism the cause must be sought elsewhere particularly in the pituitary gland. It has been referred to above. It is rather a symptom than a disease and as such a detailed repetition of its characteristics might only lead to confusion. Particular attention should be directed to pituitary dwarfism (see page 906) Frohlich's syndrome (page 897) and Simmonds' disease (page 899).

Retarded growth and sexual development may in addition occur from a variety of organic infections and other causes such as cretinism infantile myxcedema congenital heart disease birth palsy cerebra disease rickets lead poisoning congenital syphilis tuberculosis hookworm infestation pellagra etc. There have been attempts to classify the symptoms and signs of the various clinical syndromes into different groups depending upon whether the principal manifestations are morphologic or mental and to insert an intermediate or unknown group where the causes and manifestations are supposed to rest upon some unknown biochemical factor or to be associated with a perversion of intermediate metabolism.

When growth of stature is normal the pituitary gland may be exonerated. It seems most probable that the syndrome is primarily ovarian in origin. They continue to have the childish configuration of skeletal and genital development (without the secondary sexual characteristics). There is no constant nutritional pattern in other words they may be obese normal or thin.

The most common cause of amenorrhoea is pregnancy which in time reveals itself. But during the procreative period of women emotional and nutritional factors may play a prominent role. A striking example of this was observed among female internees during the last war. It has been difficult to determine which was the dominating factor but it is well known that either independently may produce this result and combined even more so. The amenorrhoea of *anorexia nervosa* is probably a summation of these factors in sequence as it frequently follows an emotional insult and precedes the in-

**ORIGIN** These examples point to the sensitive response of ovarian function in common with other physiological functions which may be grouped within the orbit of "psychosomatic" medicine (see Chapter XVI)

**Menopause**—Finally, there is the *menorrhoea* of the menopause. It must be appreciated that this is not necessarily an explosive or sudden biological event. In many instances the regularity and degree of menstrual flow may decline in proportion to estrogen production. There is however a minimal level of this below which menstruation ceases, but this does not rule out the possibility of an occasional upsurge of estrogen which may cause a moderate even to an excessive menstrual flow at irregular but diminishing frequency. The normal menopause usually begins in the midforties. Instances have been reported as early as the twenties and as late as the seventh decade. The rapidity of its completion varies from an almost explosive suddenness to a prolongation extending into years.

The symptoms and signs of the normal menopause and that artificially produced by castration or oviduction vary only in time and duration of the evolution. They may be grouped under the following.

**Menstruation** Irregularity of the menstrual periods as regards the interval, duration and quantity is usually an early sign with eventually complete cessation. Slight recurrences and continuous "spotting" should always suggest uterine cancer until proved to the contrary but this may occur during the course (and particularly after the withdrawal) of therapy with estrogenic substances.

**Vasomotor instability** is represented by hot flushes, tachycardia, palpitation, sweating, vertigo, tinnitus and syncope. Epistaxis has been considered common but is mostly associated with hypertension. The occurrence of this disturbance of circulatory function has been considered elsewhere (see page 373).

**Emotional instability** is quite characteristic of this period. Women are then subject to irritability, to worry, over trifles are exacting and suspicious, are easily aroused. These may take the form of various phobias which may even assume the proportions of hallucinations and delusions. Acute depression sometimes occurs. Sexual desire usually wanes but in some women it is maintained and may even become conspicuously increased.

**Anatomical changes** are principally confined to an atrophy of the sex organs. The ovaries become fibrotic, the uterus is reduced in size and is firmer, the vaginal glands atrophy with decreased secretion, the labia shrink and the breasts become shrivelled and flabby. An increase of weight is common.

The *diagnosis* is not difficult if a careful history and examination are carried out. It is most likely to be confused with neuroses or cardiovascular disturbances. All other organic endocrine and psychic possibilities should be excluded. Its very obviousness may permit sins of omission as it is in the fifth decade that many diseases of later life have their beginning such as diabetes mellitus, pernicious anemia, hypertension, myxedema and cancer.

The *treatment* of either spontaneous or artificial menopause sometimes offers considerable difficulties. In a general way all disturbing mental and physical factors should be eliminated. The specific treatment should be conducted along the following lines. Estrogenic substances may be administered either

by injection or by mouth. Hot flushes serve as a good criterion for following the effect of the therapy. It is probably best to begin with large doses (10 000 IU) of the estrogenic substance intramuscularly three times a week until relief is obtained, then it may be decreased until a minimal effective level is found. Some estrogenic substances are said to have a more prolonged action than others. Oral therapy with natural estrogens may be effective in milder cases or as an adjuvant to the injections. The synthetic estrogen (stilbestrol) has been widely used in certain countries recently. Its advantage is its marked activity while its disadvantage is nausea and gastrointestinal disturbances in a certain proportion of cases and more severe disturbances in a few.

As time passes improved synthetic preparations of compounds with estrogenic properties have been prepared which have no toxic effects. They are prepared in amounts of 1.25 mg per tablet under the trade names of Premarin and Konstrin. The usual dosage is 2 to 4 tablets a day but the response varies considerably from patient to patient and therefore each case must be assessed individually on the basis of trial and error in order to accomplish the best results.

It must be appreciated that there may be considerable emotional trauma inflicted by the thought that the young woman is biologically imperfect. Therefore it is often necessary to attempt to remove this inferiority by substitution therapy. A course of estrogen for a period of three to four days is given then a course of progesterone is added for ten to twelve days. This may bring about an artificial menstrual flow. Then for a period of fourteen days after it begins the therapy is withdrawn. This therapeutic cycle should be repeated for six to twelve months. On its cessation occasionally fairly normal menstrual cycles may continue even in what might have appeared to be cases of obstinate hypofunction. The cause of this is unknown. It has been suggested that it is a reverse effect upon the pituitary gland. If spontaneous menstruation does not occur after such treatment it is then optional on the part of the patient as to whether this substitution therapy should be continued. It is sometimes indicated to advise strongly that it should be continued so as to relieve to some degree or entirely the emotional trauma.

**Menorrhagia**—This term is used to designate an excessive menstrual flow. It would therefore most likely be due to an overactivity of estrogen and/or progesterone leading to abnormal endometrial hyperplasia. The occurrence of this may be related to three divisions of time from the menarche to the menopause. These are in chronological order (1) a number of years after menstruation has begun from the 14th to 20th year (2) from the 20th to 30th year and (3) from the 30th to 45th year before the menopause is complete. These are rough demarcations and must be so considered. Furthermore menorrhagia does not occur in all women by any means.

Menorrhagia in the first and third divisions would seem to rest in most instances on a similar basis. The first menstrual period does not indicate that the regular ovulation cycles have been established. In succeeding cycles the ovarian follicles may irregularly proceed to maturation but not to ovulation. Therefore estrogen may be produced but no progesterone. The endometrium will in consequence continue to pile up. There may be a series of nonovu-

lutory cycles and depending upon the number of these, so will the volume of menstrual flow when it does occur, follow an ovulatory cycle which leads to the production of progesterone. It is to be expected that if two or more nonovulatory cycles have occurred in succession the menstrual loss will be greater than if there has been only one. In the first circumstance the menstrual flow may be almost anovulatory, leading to a reduction of the hemoglobin to 40 per cent or less. After a longer or shorter period the ovulatory cycle becomes established and these occasions of excessive flow cease. This may occur irregularly with several menstrual flows normal in time and amount, and this may be followed by menorrhoea which is again followed by an excessive flow. Such may occur rarely during the greater part of the sexual life of a woman.

The final diagnosis of this condition is for as hormonal therapy is concerned must rest upon an endometrial biopsy or a study of the menstrual cells and/or the vaginal epithelium after the technique of Papanicolaou. These however are matters of special technique and the reader is referred to texts on gynecological pathology.

The treatment however is indicated in the general principles outlined above. As this is an excessively prolonged action of estrogen without progesterone to complete a normal menstrual cycle this may be accomplished by giving progesterone for 10 to 14 days before the date when menstruation would normally be expected. By this substitution therapy the normal endometrial cycle may be completed. It often happens that after this has been continued for some months (6 to 8) the cessation of progesterone therapy is followed by menstrual periods normal in time and amount.

Androgens should never be given.

Curetage of the uterus is of very doubtful value and should be reserved for diagnosis or for use in the occasional case when it would seem desirable to be sure that all abnormal hyperplastic endometrium has been removed.

The question of hysterectomy may sometimes be faced. All measures to avoid it should be avoided. It is true that the operative risk is slight but the psychological and emotional consequences are frequently of a serious character when a young woman in her upper teens or early twenties is faced with a prospect of biological inferiority.

It is obvious that the general condition of these patients should be maintained by supportive treatment as to diet, exercise and rest with regular and continuous courses of iron. It is further obvious that a thorough exploration should be made of the general physical condition especially in regard to any abnormality of the thyroid or pituitary glands.

The third division of time mentioned above it really this same process in reverse. As women approach the time of menopause it is to be expected that maturation of ovarian follicles may occur without ovulation but with a continued formation of estrogen but not of progesterone. So the menstrual cycles become irregular and excessive menstruation may occur. This however does not necessarily happen following all irregularities as even maturation of the follicles may not occur until there is complete ovarian inactivity (see Menopause page 956).

The treatment of menorrhagia at this time may follow the same lines as in the first period but with a difference. Biological usefulness of the uterus is now reaching its termination and therefore hysterectomy does not have the same implications as it had twenty years before. Further the age period for the increasing incidence of cancer is at hand. Therefore a hysterectomy may serve two purposes namely the correction of the present condition and be after the manner of prophylactic surgery. There are however occasional cases in which for some reason the risk of such an operation should be avoided or postponed then the substitution therapy mentioned above may be of value. But in such the certainty of the diagnosis must be confirmed by histological means.

The second time division is an arbitrary one and is not necessarily confined to these years but is in relation to previous pregnancies. Therefore the menorrhagia may occur irrespective of the quality of ovulation. In most cases it has a strictly anatomical basis in that the endometrium is shed in patches over a period of many days and not in a fairly uniform fashion as occurs normally. The reason for this is not known nor can it be taken for granted that this is the case without verification by biopsy when a progesterone endometrium should be found. Furthermore other anatomical lesions should be sought by a careful gynecologic examination. However the functional or estrogenic menorrhagia described above should not necessarily be excluded and should be suspected when there are periods of amenorrhea followed by excessive bleeding.

The treatment of these cases will depend upon the cause and should be decided upon after consultation with the gynecologist and endocrinologist.

Irregular uterine bleeding should always be suspected as being due to an anatomical lesion such as uterine fibrosis cancer etc. It is therefore imperative that it be given prompt attention. This is particularly the case in all women over forty but at no age should it be neglected. All diagnostic methods should be employed by experts.

**4 Sterility**—Sterility in the female has already been dealt with to some extent under hypogonadism and absence of ovulation. If however there is good reason to believe that ovulation does occur then it is a question of determining why the ovum has not reached the sperm in the first place or does not remain implanted in the prepared endometrium in the second. These problems are beyond the scope of the present text and are within the role of specialists in this subject in collaboration at times with the gynecologist. This is also intimately related to *habitual abortion* when it may be suspected that either the ova are frequently imperfect or the secretion of the corpus luteum is deficient. If local uterine anatomical abnormalities can be excluded this would appear then to be within the realm of the endocrinologist (J. C. M.)

### Developmental Abnormalities

Abnormalities of the genital organs are found in both sexes. They consist of the following: hermaphroditism and pseudohermaphroditism and cryptorchidism. In the female imperforate vagina bicornate uterus etc. are reported. These conditions are dealt with in detail in textbooks on urology and

gynecology. The anatomical findings are often confusing and the detection of the exact functional disability may rest upon a careful biochemical analysis and partition. J C M

## DISEASES OF THE PARATHYROID GLANDS

### Introduction

The parathyroid glands are four in number and normally rest behind the lateral lobes of the thyroid. Their location is not always consistent in that they may be found behind the trachea or in the anterior mediastinum. Their blood supply is derived from the inferior thyroid artery. So far as is known, these small glands, each the size of a bean, secrete a hormone which controls the calcium balance between the blood and tissues. They function independently of other ductless glands although recent evidence would suggest the influence of a pituitary factor. MacCallum and Voegtlin showed that the state of tetany which followed their removal could be symptomatically controlled by injections of calcium. Collip, in 1925, isolated the active principle of its secretion which is called *parathormone*.

With any state of hypoparathyroidism spontaneous or postoperative the blood plasma calcium drops from its normal level of 10 mg per cent with an associated rise in the plasma phosphorus. If the blood calcium falls below 7 mg per cent a syndrome known as tetany appears. Dogs which have had their parathyroid glands removed frequently develop bilateral cataract. The author has seen one such case in a man whose parathyroids were accidentally removed during subtotal thyroidectomy.

A disease of the bones is now recognized to be due to hyperparathyroidism. This is known as *osteitis fibrosa cystica* and is caused by the irregular withdrawal of calcium from the bones with the development of cystic areas. The etiological lesion is either a tumor or hyperplasia of one or more of the parathyroid glands.

### Calcium Metabolism

The normal plasma calcium is 10 mg per cent of which about 60 per cent is ionized and the remainder is bound to protein. The control of the percentage of the total calcium that is ionized is not understood. The ionized fraction is the functioning fraction in the matter of neuromuscular irritability and the deposition and withdrawal of calcium from the bones and the teeth. No method is available which is exact and practical for the determination of this ionized fraction; thus calcium determinations upon blood denote total calcium only.

The body calcium is derived from the food. The daily requirement is about 10 gram. Milk is the main source of supply and without 50 per cent of the requirement being taken in that form a deficiency is usual. Calcium absorption is variable and excretion takes place by the urine and the feces. The child excretes a greater percentage of the total by the feces than the adult. The blood calcium is remarkably constant. The balance of ionized calcium between blood plasma and tissues (bone and teeth principally) is controlled by the parathyroid hormone. A deficiency of this hormone results in

a fall of the plasma calcium with an increased bone storage and a lessened excretion in the urine. An excess of parathyroid hormone causes an elevation of blood calcium, a withdrawal from the bones and teeth and an increased excretion in the urine. A very low blood calcium (6 mg per cent) may be seen in chronic nephritis associated with low serum proteins. These patients do not have tetany because the plasma calcium deficiency occurs at the expense of the nonionized fraction which is bound to protein.

### Hypoparathyroid Function

Tetany and cataracts are the two pathological states known to follow deficient parathyroid function. Tetany is a clinical syndrome which may have several causes.

#### Tetany (Spasmophilia)

**Definition**—Tetany is a state of increased irritability of the neuromuscular control. In its mildest forms it can be detected by the electrical reactions of muscles, and by abnormal responses characteristic of this state. In its more active form spasms or cramps of muscle groups and tetanic convulsions occur.

**Etiology**—The causes of tetany fall into two main groups: (1) where there is a lowering of the physiologically active serum calcium, and (2) where an alkalosis with an increase of the pH of the blood plasma develops. The ionized serum calcium is lowered by (1) removal of the parathyroids, (2) administration of all saline phosphates ( $\text{Na HPO}_4$ ), and (3) in certain types of rickets and osteomalacia. An alkalosis with an increase of the pH of the blood plasma may occur from (1) hyperpnea, (2) persistent vomiting, and (3) the administration of excessive alkali (see Alkalosis, page 866).

Parathyroid tetany follows removal of the parathyroid glands which may occur accidentally at the time of thyroidectomy. The blood calcium falls and there is a concomitant rise in the inorganic phosphorus. Excessive intake of alkaline phosphates ( $\text{Na HPO}_4$ ) will likewise lower the blood calcium and raise the phosphorus. Infantile tetany occurs in children with rickets and hypocalcemia. Osteomalacia or adult rickets (see page 803) also may show hypocalcemia leading to tetany. In all of these low blood calcium types of tetany it is the ionized fraction of the serum calcium that is reduced. When the total blood calcium reaches a level of 7 mg per cent (normal 10 mg per cent) tetany may appear. In diseased states where there is a great lowering of the serum proteins the total blood calcium may fall even to 6 mg per cent without tetany because the loss occurs at the expense of the fraction bound by the serum proteins which is not physiologically active.

Hyperpnea may be voluntary, follow hot baths or occur in hysterical patients. It results in a primary  $\text{CO}_2$  deficit of the blood or a noncompensated gaseous alkalosis and may progress to an abnormal increase of the pH of the blood. Persistent vomiting causes an excessive loss of hydrochloric acid and consequently a reduction of the blood chlorides, the latter being compensated for by an increase of the plasma bicarbonate and an alkalosis (gastric tetany). This is commonly seen in pyloric obstruction. Administration of an excessive amount of sodium bicarbonate also may cause an increase of the plasma pH.

The  $\text{CO}_2$  capacity of the blood may rise to over 100 volumes per cent. Tetany occurs with alkalosis (relative or absolute) when the pH of the blood reaches 7.6. In the low calcium tetanias there is no evidence of an alkalosis.

**Symptoms and Signs**—Mild or latent tetany may have few symptoms, but certain signs can be elicited. Of these, Erb's sign is the most constant. The motor nerve in tetany will respond to an electrical stimulus with a far weaker current than is required to produce a minimal reaction in a normal person. Normally the cathodal opening response requires more than 11 milliamperes while in tetany a response is obtained with less than 5 milliamperes. Also tetanic contraction can be obtained with a weaker current on anodal opening than with anodal closure. This is the reverse of the normal response. Chvostek's and Trousseau's signs are also indicative of tetany. The former is a spasm of innervated muscles by tapping the facial nerve just anterior to the ear at the point where it emerges from the stylomastoid foramen. The latter is a typical tetanic spasm of the muscles of the forearm and hand elicited by compression of a nerve trunk on occlusion of the arterial blood supply in the upper arm. The hand assumes a rigid flexed posture with the fingers flexed at their metacarpophalangeal joints and the thumb adducted (Fig. 36).

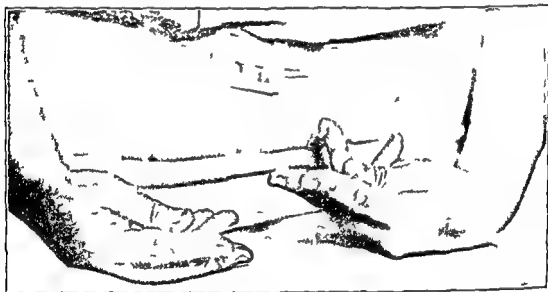


Fig. 36.—Parathyroid tetany showing Trousseau's sign.

When tetany is active these muscular spasms occur spontaneously. All voluntary muscles may undergo clonic or tonic contractions and muscle cramps and stiffness are common. With involvement of the glottis breathing is difficult and noisy (laryngismus stridulus). Glottic involvement occurs mainly in children, and is accompanied by severe cyanosis and complete cessation of respiration may follow. The diaphragm may also be affected producing severe epigastric pain and with spasm of the intercostal muscles seriously interfere with respiration. In fact no muscle may be exempt including the esophagus, bladder, vagina and intestines. Tetany in its severest form may cause generalized convulsions and death.



TABLE VII

ANALYTICAL FINDINGS IN VARIOUS TETANIES AND RELATED DISORDERS

(From Cecil Text Book of Medicine 6th edition W B Saunders Company Philadelphia 1933 page 144.)

DISEASE	BLOOD PLASMA VALUES				EXCRETION DURING LOW CALCIUM DIET			
	CALCIUM	TOTAL PHOSPHORUS	PH	PHOSPHATASE	URINE		FEACES	
					CA.	P.	CA.	P.
Tetany due to parathyroid deficiency	low	high	normal		low	low	normal	normal
Hypoparathyroidism	high	low	normal	high	high	high	normal	normal
Steatorrhea—difficulty in absorbing calcium from the intestines	normal or low	low	normal	normal or slightly high	low	high	high	normal
Obtundity from leukemia and rickets	normal or low	low	normal	high	low	low	low	low
Hypertetany	normal	normal	normal	high	very high	very high	high	high
Agita disease (Osteitis deformans)	normal	normal	normal	very high	No marked variation			
Latent tetany	normal	normal	increased					
Hyperventilation	normal	normal	increased					
Excessive bicarbonate ingestion	normal	normal	increased					

**Diagnosis**—Tetany offers difficulty in diagnosis only in a latent form Chvostek's and Trousseau's signs may be absent but Erb's sign will always be present The blood will show the lowering of the serum calcium or a state of alkalosis It is differentiated from tetanus strychnine poisoning, and hysteria It must always be remembered that tetany is a sign of a systemic disturbance and not a disease in itself

**Prognosis**—The prognosis largely depends upon the causal factor of the tetany When this is correctly recognized it can be relieved by parathyroid extract calcium salts or acid administration It is usually possible to detect and remove the basic cause if it be carefully sought and thus a cure may be established

**Treatment**—In the treatment of tetany recognition of the disturbed physiology is essential All forms of tetany improve temporarily with acid therapy on account of the acidosis reducing the irritability of the neuromuscular control Ammonium or calcium chloride 1 to 8 grams a day will be effective These acid producing salts have a rapid effect upon the symptoms and increase calcium absorption By reduction of the alkalinity of the blood relief can be obtained with no change in the plasma calcium Calcium chloride is especially effective in that it supplies calcium in addition to reducing the blood alkalinity To cause more lasting results treatment must be specific

The following procedures are recommended

### 1 Tetany Due to Low Blood Calcium.—

**A Parathyroid Tetany**—For rapid relief of symptoms ammonium or calcium chloride by mouth or calcium gluconate intravenously is usually promptly efficacious Calcium lactate in large doses 4 to 12 grams a day,

The  $\text{CO}_2$  capacity of the blood may rise to over 100 volumes per cent. Tetany occurs with alkalosis (relative or absolute) when the pH of the blood reaches 7.6. In the low calcium tetanias there is no evidence of an alkalosis.

**Symptoms and Signs**—Mild or latent tetany may have few symptoms, but certain signs can be elicited. Of these Erb's sign is the most constant. The motor nerve in tetany will respond to an electrical stimulus with a far weaker current than is required to produce a minimal reaction in a normal person. Normally the cathodal opening response requires more than 6 milliamperes while in tetany a response is obtained with less than 5 milliamperes. Also tetanic contraction can be obtained with a weaker current on anodal opening than with anodal closure. This is the reverse of the normal response. Chvostek's and Trousseau's signs are also indicative of tetany. The former is a spasm of innervated muscles by tapping the facial nerve just anterior to the ear at the point where it emerges from the stylomastoid foramen. The latter is a typical tetanic spasm of the muscles of the forearm and hand, elicited by compression of a nerve trunk on occlusion of the arterial blood supply in the upper arm. The hand assumes a rigid flexed posture with the fingers flexed at their metacarpophalangeal joints and the thumb adducted (Fig. 36).

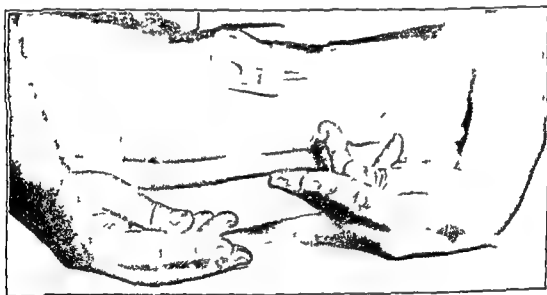


Fig. 36.—Parathyroid tetany showing Trousseau's sign.

When tetany is active these muscular spasms occur spontaneously. All voluntary muscles may undergo clonic or tonic contractions and muscle cramps and stiffness are common. With involvement of the glottis breathing is difficult and noisy (laryngismus stridulus). Glottic involvement occurs mainly in children and is accompanied by severe cyanosis and complete cessation of respiration may follow. The diaphragm may also be affected producing severe epigastric pain and with spasm of the intercostal muscles seriously interfere with respiration. In fact no muscle may be exempt, including the esophagus, bladder, vagina and intestines. Tetany in its severest form may cause generalized convulsions and death.

glands. There may be an adenomatous growth of one or more glands or a general state of hyperplasia. Rarely has it been possible to palpate the hyperplastic glands or a tumor.

**Symptoms and Signs**—The onset is usually insidious with general lassitude, weakness and pains in the bones. Later there is loss of appetite with a low blood pressure. Physical examination may disclose tender areas on the long bones. The laboratory findings are of special importance. The blood calcium is raised (normal 10 m. per cent) to a level of even 15 mg. per cent in severe cases. There is an associated lowering of the blood phosphorus and an increased excretion of calcium in the urine. Thus mobilization of calcium



Fig. 266—X ray of hand in a case of telic fibrous cysts due hyperparathyroid function

from the bones results in thinning of the skeleton and patchy absorption of the bone trabeculae with the development of the characteristic bone cysts which can be seen by x ray. The bone absorption results in an increased activity on the part of the bone osteoclasts with the formation of giant celled bone tumors. The increased plasma calcium concentration often leads to the formation of both renal and biliary calculi. The hypercalcemia in time results in premature arteriosclerosis and chronic nephritis with nonprotein nitrogen retention.

**Diagnosis**—The diagnosis may be suggested by the history and the physical examination but it ultimately depends upon the laboratory findings. In the meantime the condition may be called myalgia, lumbago, neuritis, arthritis,

is of value in chronic cases. Parathyroid extract (parathormone) 50 units a day, will raise the serum calcium at the expense of the calcium stored in bones and other depots. The physiological effect starts in four hours, when given intramuscularly and lasts for twenty four hours. If continued for a protracted period of time it is capable of producing hypercalcemia. Continued dosage must be checked regularly by determining the blood calcium. With protracted administration a tolerance is acquired which necessitates the use of increasing dosage. Recently dihydrotachysterol (A.T. 10) has been used in parathyroid tetany with excellent results. It is given by mouth in doses of 2 cc daily, but hypercalcemia must be looked for.

**B Alkaline Phosphate Tetany**—This type is largely experimental, and immediate relief of symptoms can be obtained by discontinuance of the basic phosphate and the administration of acids.

**C Infantile Tetany (with Rickets)**—Any procedure that will produce an acidosis will relieve the symptoms. Ammonium and calcium chloride acid ammonium phosphate, hydrochloric acid, and a ketogenic diet have been used. Methods that raise the blood calcium, parathyroid extract or calcium gluconate are temporarily effective. Institution of prompt treatment to cure the rickets is essential. For this vitamin D in irradiated ergosterol or a cod liver oil concentrate may be used. Ultraviolet light and sunlight are most helpful.

**D Tetany in Osteomalacia**—Treatment should be the same as for tetany with rickets.

## 2 Alkalosis with Tetany—

**A Hyperpnea Tetany (Uncompensated Gaseous Alkalosis)**—Treatment depends upon alleviating or removing the neurotic causes of the overventilation, and rebreathing a 5 per cent  $\text{CO}_2$  and oxygen mixture. Acidifying measures will reduce the blood alkalinity but do not strike at the fundamental cause (see Chapter XVI).

**B Gastric Tetany (Loss of Chlorides)**—Ammonium chloride or hydrochloric acid in therapeutic doses will give prompt relief. Intravenous hypertonic (5 per cent) NaCl solutions are helpful. Cure will depend upon relief of the basic cause: pyloric stenosis, intestinal obstruction, paralytic ileus, etc.

**C Tetany from excessive sodium bicarbonate therapy** is promptly relieved by the cessation of this and the intravenous injection of hydrochloric acid in 0.5 per cent solution.

## Parathyroid Cataract

The incidence of bilateral cataracts in the dog after removal of the parathyroid glands is high. In man it is a rare complication of parathyroid deficiency and once established it cannot be influenced by medical means. Extraction of the cataracts after they have developed sufficient maturity will restore vision. The parathyroid deficiency should receive appropriate treatment.

## Hyperparathyroidism (Osteitis Fibrosa Cystica)

A bone disease termed osteitis fibrosa cystica first described by von Recklinghausen, is now known to be due to an excessive function of the parathyroid

toms and signs are referable to pressure effects from the tumor itself. The condition of macro-genitosomia precox in children is related to a pineal tumor. It is not known whether this sexual precocity is the result of increased or decreased functional activity of the tumor cells.

The pineal tumors in their early stages of development frequently compress the aqueduct of Sylvius with increase of pressure in the lateral ventricles producing internal hydrocephalus. Ringing in the ears, headache, nausea, projectile vomiting, and papilloedema follow undoubtedly due to increased intracranial pressure. Further symptoms and findings depend upon the area of the brain involved, and the cranial nerves compressed. The presence in a child of the findings characteristic of a brain tumor as well as sexual precocity would justify the conclusion of the presence of a pineal tumor.

Due to their location surgical removal is difficult but may be successful in the encapsulated cases. Unfortunately the majority are infiltrative. x-ray therapy may be tried as a palliative measure.

### DISEASES OF THE THYMUS GLAND

The thymus gland is of epithelial origin and derived embryologically from the third and fourth branchial clefts. It is located in the anterior mediastinum and weighs at birth about 12 grams. It increases in size up to puberty (weight 37 grams) and subsequently undergoes a gradual atrophy.

The exact function of the thymus gland is unknown. No growth disturbances have ever been proved to be connected with a primary lesion.

Experimentally in fowls, Soli observed that thymectomy caused eggs to be laid without calcium in the shells. Thymus feeding to such thymectomized hens restored a normal shell formation. This work was confirmed by Riddle. Rowntree has reported remarkable observations upon the results of injection of successive generations of rats with a thymus extract. After the third generation the young are born in a state of precocity and their early growth and development are greatly accelerated. Sexual maturity occurs early and fertility is increased. When adult growth is reached the animals do not differ from the normal.

**Pathological Anatomy**—Hypertrophy and hyperplasia of the thymus have been found. After puberty the thymus undergoes regression therefore a relatively hypertrophied gland in adult life may be an arrest only of this normal cycle. Tumors are the best understood primary thymus lesion. They may be benign but carcinoma, sarcoma and thymoma are relatively common. Lymphosarcoma is the most frequent arising from the adult cell of the thymus which is of the order of a lymphocyte.

### Thymus Tumors

Benign and malignant tumors of the thymus cause symptoms of pressure in the anterior mediastinum. Cyanosis of the upper extremities, dilated veins over the upper chest, tracheal obstruction, esophageal obstruction and cardiac arrhythmias from vagus and sympathetic irritation are the main signs. Per-

and a host of other simple conditions which are not diagnoses but confessions of neglect. An elevated blood calcium with a lowered plasma phosphorus associated with bone cysts, and possibly renal stones, makes the diagnosis definite. Certain cases have cycles of hyperparathyroidism with periods when the blood calcium is only slightly elevated. A calcium balance well controlled will show the excess urinary excretion.

**Complications and Prognosis**—The natural history of the disease is to gradually withdraw so much calcium from the skeleton that the bones become thinned and spontaneous fractures follow. Even collapse of a vertebra with pressure on the nerve roots may occur. Renal and biliary calcium stones are usual and lead to infection, which is particularly important as renal insufficiency may follow.

Early diagnosis and removal of the adenoma from the parathyroid gland may completely arrest the hyperparathyroidism. Symptoms disappear and the bone changes and the blood calcium and phosphorus tend to revert to the normal. Accordingly the prognosis rests upon early diagnosis and the successful finding of a parathyroid lesion and its removal. Otherwise the disease will progress.

In addition to the above lesions there has been described by Selye a condition of edema and scleroderma due to moderate parathyroid hyperfunction. It would seem to have a bearing in man upon certain indefinite dermatologic trophic and vascular disturbances which are not as yet thoroughly understood particularly in relation to certain deficiency syndromes.

**Treatment**—Successful treatment depends entirely upon finding the parathyroid lesion and its removal. More than one parathyroid may be involved. If extensive parathyroid removal is necessary, parathyroid tetany may follow but usually only temporarily. Provided two of the parathyroid glands remain a normal function can be expected. During the period of redeposition of calcium and phosphorus in the depleted bones a diet high in calcium and phosphorus should be given.

## DISEASES OF THE PINEAL GLAND

The pineal gland is about 6 mm long and lies just over the midbrain in the median line. Its physiology is not known. Rather early in life it tends to become calcified thereby casting a shadow above and behind the sella turcica. Rowntree has injected pineal gland extracts into rats with some evidence of abnormal development. The offspring have shown an excessive growth of hair but tend to be dwarfed.

### Pineal Tumors

Most of the clinical knowledge concerning the pineal gland has been assembled from a study of cases with pineal tumors. These tumors may be of varied nature, infiltrating or encapsulated, malignant or benign. The infiltrating types are the more numerous. In children pineal tumors are infrequently associated with a state of sexual precocity while in adults the symp-

cussion shows a broadening of the sternal dullness and x ray confirms this by revealing an enlarged shadow in the anterior mediastinum

**Treatment**—Treatment is unsatisfactory. X ray therapy will cause a temporary decrease in size with symptomatic improvement but the fatal outcome is only delayed

### **Status Thymicolymphaticus**

Several decades ago great interest was aroused in the autopsy finding of an enlarged thymus in an infant that died suddenly. It was supposed to result from the infant's being suffocated by the enlarged thymus although signs of suffocation were not demonstrable. As a consequence the chests of large numbers of children were x rayed shortly after birth and if the thymus shadow appeared enlarged they were given x ray treatment. Some shrinkage of the thymus shadow followed but the controls if any did not support any specific effect. More recently the validity of this interpretation has been seriously doubted. There is little evidence today that sudden deaths without symptoms are due to enlargement of the thymus gland.

The position of *status thymicolymphaticus* as a clinical condition has given rise to much controversy. The principal difficulty has rested upon the confusion of definitions. There seems little doubt that there is a clinical syndrome with the following characteristics. The infant or child is well nourished and the skin thin and smooth. There is general lymphoid hyperplasia of the follicles of the tongue, the tonsils, lymphadenopathy, splenomegaly, susceptibility to catarrh of the mucous membranes. The thymus may be large but this must be judged in relation to its normal evolution. These children are prone to infections and a hypoglycemia has been reported.

The anatomical changes confirm the clinical findings but in addition there may be found diffuse lymphoid infiltration of the tissues and the bone marrow may be hyperplastic and contain diffuse and focal lymphoid deposits.

It would seem best to consider this condition as constitutional rather than as a disease entity until much more is known concerning it.

Sudden deaths may occur and are so often associated with anesthetics, serum injections and arsenic therapy that caution should be exercised in this condition in all unusual procedures. These deaths should not be laid at the door of an enlarged thymus unless symptoms of suffocation are definitely present. If the thymus shadow by x ray does appear definitely enlarged irradiation may be employed but should not be considered as specific.

### **CAROTID BODY**

#### **(Carotid Glands and Carotid Sinus)**

This combination of nervous and chemical sensitive receptors in the aorta and at the bifurcation of the carotid arteries is undoubtedly an important factor in the physiologic regulation of the body. These functions have been investigated extensively by experimental physiologists but as yet their role in diseases of man is but little understood.

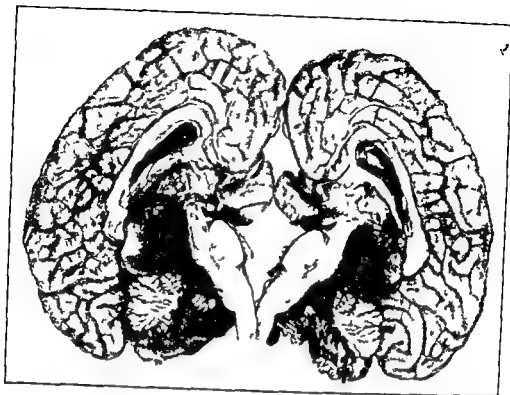


Fig 367

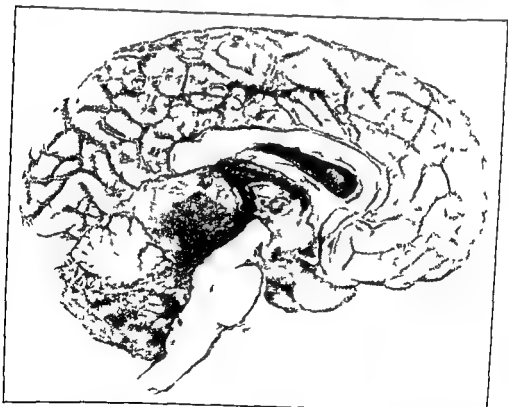


Fig 368

Fig 367—Photograph of a coronal section of an encapsulated pineal tumor in a boy of fourteen years. Complete compression of the aqueduct of Sylvius with hydrocephalus. The syndrome of macrogenitosomia precox was not present.

Fig 368—Photograph of an anteroposterior section of an encapsulated pineal tumor in a boy of fourteen years same case as shown in Fig 367.



cussion shows a broadening of the sternal dullness, and x ray confirms this by revealing an enlarged shadow in the anterior mediastinum

**Treatment**—Treatment is unsatisfactory. X ray therapy will cause a temporary decrease in size with symptomatic improvement but the fatal outcome is only delayed

### **Status Thymicolymphaticus**

Several decades ago great interest was aroused in the autopsy finding of an enlarged thymus in an infant that died suddenly. It was supposed to result from the infant's being suffocated by the enlarged thymus although signs of suffocation were not demonstrable. As a consequence the chests of large numbers of children were x rayed shortly after birth and if the thymus shadow appeared enlarged they were given x ray treatment. Some shrinkage of the thymus shadow followed but the controls if any did not support any specific effect. More recently the validity of this interpretation has been seriously doubted. There is little evidence today that sudden deaths without symptoms are due to enlargement of the thymus gland.

The position of *status thymicolymphaticus* as a clinical condition has given rise to much controversy. The principal difficulty has rested upon the confusion of definitions. There seems little doubt that there is a clinical syndrome with the following characteristics. The infant or child is well nourished and the skin thin and smooth. There is general lymphoid hyperplasia of the follicles of the tongue, the tonsils, lymphadenopathy, splenomegaly, susceptibility to catarrh of the mucous membranes. The thymus may be large but this must be judged in relation to its normal evolution. These children are prone to infections and a hypoglycemia has been reported.

The anatomical changes confirm the clinical findings but in addition there may be found diffuse lymphoid infiltration of the tissues and the bone marrow may be hyperplastic and contain diffuse and focal lymphoid deposits.

It would seem best to consider this condition as constitutional rather than as a disease entity until much more is known concerning it.

Sudden deaths may occur and are so often associated with anesthetics, serum injections and arsenic therapy that caution should be exercised in this condition in all unusual procedures. These deaths should not be laid at the door of an enlarged thymus unless symptoms of suffocation are definitely present. If the thymus shadow by x ray does appear definitely enlarged irradiation may be employed but should not be considered as specific.

### **CAROTID BODY**

#### **(Carotid Glands and Carotid Sinus)**

This combination of nervous and chemical sensitive receptors in the aorta and at the bifurcation of the carotid arteries is undoubtedly an important factor in the physiologic regulation of the body. These functions have been investigated extensively by experimental physiologists but as yet their role in diseases of man is but little understood.

The depressor or aortic nerve (a vagal branch), described by Ludwig and Cyon in 1866, and the carotid sinus innervated by a branch of the glossopharyngeal nerve, described by Hering in 1924, form undoubtedly an essential link in the regulation of the circulation and in mammals a less critical one of respiration.

The carotid sinuses are localized enlargements in the wall of the carotid arteries at their bifurcation. They contain nervous receptors, whereas the carotid body is a small chromophil collection which is sensitive to chemical stimuli. The intimate association of these two structures is not without significance.

The carotid sinus is influenced by the pressure within the carotid arteries as is the aortic nerve by that within the aorta. As the pressure rises, there is an increased volley of impulses generated in the sinus, and as a result there is a reflex relaxation of the arterioles and probably also the capillaries and the large veins and a bradycardia. This is general, and there is no evidence that this is in any way local. As a result there is a compensatory fall in peripheral resistance in order to maintain a proper circulatory equilibrium. On the other hand, there is no evidence that a low arterial pressure alone stimulates any nervous receptors to raise the peripheral resistance and thus the blood pressure. The reaction to a fall in blood pressure, however, is a constriction in all types of blood vessels, a tachycardia, an increased outpouring of adrenalin and a contraction of the large veins.

Denervation (or anesthetizing) of the carotid sinuses produces a permanent elevation of blood pressure which may be quite alarming. There are tachycardia, extrasystoles, bigeminy, electrographic changes and cardiac hypertrophy.

The chemical and nervous control of respiration has already been discussed (see page 324) and reference was incidentally made to the carotid body. It is doubtful whether within physiological limits the carotid glands as chemical receptors influence respiration in mammals. Experimentally asphyxia, oxygen lack and  $\text{CO}_2$  excess lead to respiratory stimulation. Section of the sinus and carotid nerves may lead to hyperpnea in some dogs, but it is not constant nor persistent unlike the hypertension and tachycardia which are. The most important finding in regard to respiration is the response of these structures to chemical stimulation by reduced oxygen tension and by the fixed acids but not by  $\text{CO}_2$  excess and by such drugs or poisons as lobeline, nicotine, cyanides and sulfides.

The application of these physiological observations to diseases or syndromes in man are not as yet at all clear. Hyperactivity or hypersensitivity give a clear cut reaction. There are acute hypotension, bradycardia, bradypnea and unconsciousness. This result may be induced in certain persons by wearing a tight collar or neckband or even by pressure or stroking the skin over the anterior triangle of the neck. It is a cause of syncope which is often overlooked.

The contrary effect of paroxysmal or constant hypertension, tachycardia or hyperpnea has not as yet been recognized as a clinical syndrome although there are some who claim that such is the case. Atheromatous degeneration

of the carotid artery in the region of the sinus has been accused of producing such an effect. This must await verification. In fact this whole subject in medicine has yet to be properly explored.

Christie has demonstrated in extract of a carotid gland tumor in man to contain a thermostable vasodepressor principle in high concentration. Its action on the blood pressure, the pulse rate and the virgin uterus was directly opposite to that of adrenalin.

### Tumors of the Carotid Gland

Tumors of the carotid gland are rare. They may be benign or malignant. Their types vary as those arising from the medulla of the adrenal glands. Neuroblastomas and paragangliomas are malignant while ganglioneuromas are benign. A tumor of the carotid gland has certain clinical characteristics that are helpful in diagnosis. They are movable laterally but not vertically. They are single nodules, transmit an impulse from the adjacent arteries, cause bulging of the pharyngeal wall and are of slow growth. Removal has been accomplished. Paragangliomas are composed of the chromaffin type of cell and are sometimes associated with intermittent paroxysmal hypertension.

### References

#### *Pituitary Gland*

- Anderson, E. M. and Collip J. B. Thyrotropic Hormone of Anterior Pituitary. *Proc Soc. Exper. Biol. & Med.* 30: 650, 1933.
- Collip J. B. Chemistry and Physiology of Anterior Pituitary Hormones. *Trans. Congress Am. Physicians & Surgeons* 15: 47, 1933.
- Collip J. B., Anderson E. M. and Thomson D. L. The Adrenotropic Hormone of the Anterior Pituitary Lobe. *Lancet* 2: 347, 1933.
- Cushing H. The Basophil Adenomas of the Pituitary Body and Their Clinical Manifestations. *Bull. Johns Hopkins Hosp.* 30: 137, 1932.
- Cushing H. The Pituitary Body and Its Disorders. Philadelphia, 1912. J. B. Lippincott Co.
- Evans H. M. Function of the Anterior Hypophysis. The Harvey Lectures, Ser. XIX. Philadelphia, 1925. J. B. Lippincott Co.
- Farquharson, H. F. and Graham D. Cases of Simmonds's Disease. *Tr. A. Am. Physicians* 48: 150, 1931.
- Stiehl B. L. The Diuretic and Osmotic Action of Pituitary Extract. *Am. J. Physiol.* 79: 89, 1926-27.

#### *Thyroid Gland*

- DaBou H. F. Cecil's Textbook of Medicine, ed. 3. Philadelphia, 1933. W. B. Saunders Co. p. 1211.
- Harington C. B. and Barger G. Chemistry of Thyroxine. Constitution and Synthesis of Thyroxine. *Biochem. J.* 21: 169, 1927.
- Marine D. Etiology and Prevention of Simple Goiter. *Medicine* 3: 403, 1924.
- Marine D. Iodine in the Treatment of the Thyroid Gland. *Medicine* 5: 127, 1927.
- Means J. H. and Richardson H. P. Diseases of the Thyroid. Oxford Monographs on Diagnosis and Treatment. New York, 1929. Oxford Press.
- Hummer H. S. Results of Administering Iodine to Patients Having Exophthalmic Goiter. *J. A. M. A.* 80: 1900, 1923.
- Rienhoff W. F. A New Conception of Some Morbid Changes Occurring in Diseases of the Thyroid Gland. *Medicine* 10: 107, 1931.
- Rienhoff W. F. Involutional or Regressive Changes in the Thyroid Gland in Cases of Exophthalmic Goiter, etc. *Arch. Surg.* 13: 391, 1908.

*Parathyroid Gland*

- Aub, J C Calcium and Phosphorus Metabolism The Harvey Lectures, p 151 1928 29
- Bauer, W Hyperparathyroidism A Distinct Disease Entity J Bone & Joint Surg 15 135 1933
- Collip J B Extraction of a Parathyroid Hormone Which Will Prevent or Control Parathyroid Tetany, and Which Regulates Level of Blood Calcium J Biol. Chem. 63 395, 1925
- Collip J B Parathyroid Hormone and Its Physiological Action Ann. Clin. Med. 4 219 1925
- Hunter, D and Turnbull, H M Hyperparathyroidism, Generalized Osteitis Fibrosa with Observations Upon Bones, Parathyroid Tumours, and Normal Parathyroid Glands. Brit J Surg 19 203, 1931 32
- MacCallum, W G and Voegtlin C On the Relation of Tetany to the Parathyroid Gland and Calcium Metabolism J Exper Med 11 118 1909
- Thomson, D L and Collip J B The Parathyroid Glands, Physiol Rev 12 309, 19 32

*Suprarenal Gland*

- Brenner, O Addison's Disease with Atrophy of the Cortex of the Suprarenals Quart. J Med 22 121, 1928 29
- Hartman, F A, and Brownell K A The Hormone of the Adrenal Cortex Science 72 70, 1930
- Loeb R F Atchley, D W, et al On the Mechanism of Sodium Depletion in Addison's Disease Proc Soc Exper Biol & Med 31 130, 1933 34
- Loeb, R F, and Atchley D W Significance of Salt in Treatment of Addison's Disease M Clin North America 17 1317 1934
- Loeb R F Atchley D W and Stahl J Role of Sodium in Adrenal Insufficiency I A M A 104 2149, 1935
- Lougoff J M and Stewart G N Suprarenal Cortical Extracts in Suprarenal Insufficiency J A M A 92 1569, 1929
- Swingle W W and Pfaffner J J The Revival of Comatose Adrenalectomized Cats with an Extract of the Suprarenal Cortex Science 72 75 1930
- Swingle W W Pfaffner J J et al The Function of the Adrenal Hormone and the Cause of Death from Adrenal Insufficiency Science 77 53 1933
- Thorn George W The Diagnosis and Treatment of Adrenal Insufficiency Springfield Ill 1949 Charles C Thomas

*Genitals*

- Blair E M Endometrial Hyperplasia A Clinical Entity Canad M A J 35 603 1956
- Cameron, A T Recent Advances in Endocrinology London, 1933 J & A Churchill, Ltd
- Clauberg, C Die weiblichen Sexualhormone Berlin 1933, Julius Springer
- deAllende I I C Shorr E and Hartman C G A Comparative Study of the Vaginal Smear Cycle of the Rhesus Monkey and the Human Carnegie Institution of Washington Publication 33 Contributions to Embryology 31 1 1943
- Fagle, E T Smith P E and Shelesnyak M C Role of Estrin and Progesterin in Experimental Menstruation With Special Reference to Complete Ovulatory Cycle in Monkeys and Human Beings Am J Obst & Gynec 29 181 1935
- Kurczok, H The Endocrines in Obstetrics and Gynecology Baltimore 1931 Williams & Wilkins Co
- Papanicolaou G N and Traut H Diagnosis of Uterine Cancer by the Vaginal Smear The Commonwealth Fund New York 1943
- Robson, J M Recent Advances in Sex and Reproductive Physiology London 1934 J & A Churchill, Ltd.

Zondek H Die Hormone des Ovariums und des Hypophysenvorderlappens Berlin 1931  
Julius Springer

*Thymus Gland*

Rowntree L G Clark J H, and Hanson A M Biological Effect of Thymus Extract  
(Hanson) etc Arch Int Med 56 1 1930

*Pineal Gland*

Rowntree L G Clark J H et al Biological Effects of Pineal Extract (Hanson)  
etc J A M A 106 3:0 1930

*Carotid Gland*

Christie, R V Function of the Carotid Gland I The Action of Extracts of a Carotid  
Gland Tumour in Man, Endocrinology 17 491 1933

# CHAPTER XV

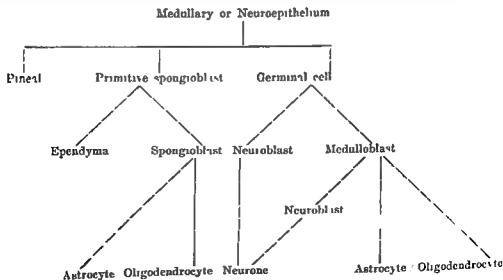
## DISEASES OF THE NERVOUS SYSTEM

J N PETERSEN, II Sc, M D, C M

### INTRODUCTION

The union of male and female germinal cells results in a unicellular fertilized ovum which has the potentialities of all the tissues of the adult individual. The development of this fertilized ovum takes place by cell division and differentiation, and with progressive differentiation the potentialities of the dividing cell groups become progressively reduced. The earliest differentiation is into the three primary layers of ectoderm, mesoderm, and endoderm, and it is from the outermost of these or the ectoderm, that the nervous system develops.

The first step in this development is the formation of the neural or medullary plate, a localized thickening in the middorsal region of the long axis of the growing embryo (Fig. 369). The cells of this plate undergo division which is most marked at its lateral borders, and because of this the center of the plate becomes depressed to form the neural groove. As the groove increases in depth, its dorsolateral margins gradually approach one another until finally an ectodermal tube becomes separated from the remainder of the growing ectoderm and lies ventral to it. This neural tube is the primitive central nervous system. At the junction of neural ectoderm and general ectoderm, a further group of cells differentiates to form the neural crest from which those nerve cells which lie outside the central nervous system develop. The neural tube also differentiates into three layers (Fig. 370) (1) an inner ependymal layer in which are located the actively dividing germinal cells (2) a middle mantle layer made up of neuroblasts and spongioblasts and (3) an outer marginal zone consisting mostly of nerve fibers. Without indicating all the intermediate steps the cellular development from the inner ependymal layer proceeds as follows (modified from Bailey)



Lining the neural tube inside and outside are the internal and external limiting membranes

The loose mesenchymal or mesodermal tissue surrounding the neural tube gives rise to the meninges, the skull and vertebral column, and also to migratory cells which invade the central nervous system and become microglia. In addition it is by invasion of mesodermal elements that the blood vessels of the central nervous system are formed.

In the earthworm each segment of the nervous system is almost identical to all other segments and each is a complete unit in itself. As animal life in

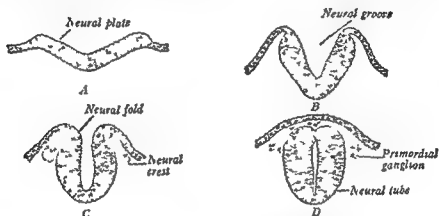


Fig 369—The development of the neural tube from the ectoderm. (From Arey: *Developmental Anatomy*, W. B. Saunders Co., Philadelphia.)

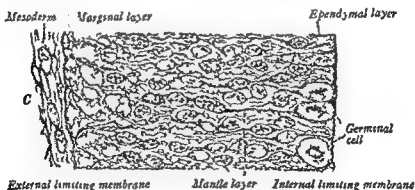


Fig 370—The cellular development of the neural tube. (After Harle, in Arey: *Developmental Anatomy*, W. B. Saunders Co., Philadelphia.)

increases in complexity and ascends in the scale of evolution, newer functions come to be located in the anterior end of the neural tube the growth of which becomes much more rapid and is complicated by the formation of flexures (Fig 371). It is from this increased growth and differentiation at the head end and the allocation of newer functions to this region that the brain is formed. The remainder of the neural tube retains much more its original conformation and becomes the spinal cord. The lumen of the tube persists as the central canal of the cord and the ventricles of the brain.

The structural and functional unit of nerve tissue is the neurone which consists of the nerve cell and its processes (Fig 372). The cells vary in size

# CHAPTER XV

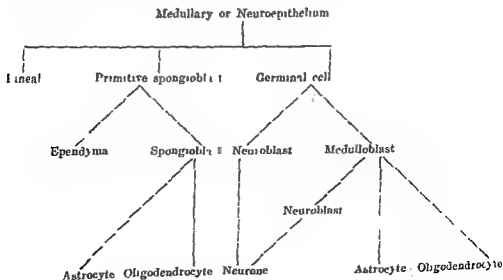
## DISEASES OF THE NERVOUS SYSTEM

J N PETERSEN, B Sc, M D, C M

### INTRODUCTION

The union of male and female germinal cells results in a unicellular fertilized ovum which has the potentialities of all the tissues of the adult individual. The development of this fertilized ovum takes place by cell division and differentiation, and with progressive differentiation the potentialities of the dividing cell groups become progressively reduced. The earliest differentiation is into the three primary layers of ectoderm, mesoderm, and endoderm, and it is from the outermost of these, or the ectoderm, that the nervous system develops.

The first step in this development is the formation of the neural or medullary plate, a localized thickening in the middorsal region of the long axis of the growing embryo (Fig 369). The cells of this plate undergo division which is most marked at its lateral borders, and because of this the center of the plate becomes depressed to form the neural groove. As the groove increases in depth its dorsolateral margins gradually approach one another until finally an ectodermal tube becomes separated from the remainder of the growing ectoderm and lies ventral to it. This neural tube is the primitive central nervous system. At the junction of neural ectoderm and general ectoderm, a further group of cells differentiates to form the neural crest from which those nerve cells which lie outside the central nervous system develop. The neural tube also differentiates into three layers (Fig 370) (1) an inner ependymal layer in which are located the actively dividing germinal cells, (2) a middle mantle layer made up of neuroblasts and spongioblasts and (3) an outer marginal zone consisting mostly of nerve fibers. Without indicating all the intermediate steps the cellular development from the inner ependymal layer proceeds as follows (modified from Bailey)





Lining the neural tube inside and outside are the internal and external limiting membranes

The loose mesenchymal or mesodermal tissue surrounding the neural tube gives rise to the meninges the skull and vertebral column and also to migratory cells which invade the central nervous system and become microglia. In addition it is by invasion of mesodermal elements that the blood vessels of the central nervous system are formed.

In the earthworm each segment of the nervous system is almost identical to all other segments and each is a complete unit in itself. As animal life in

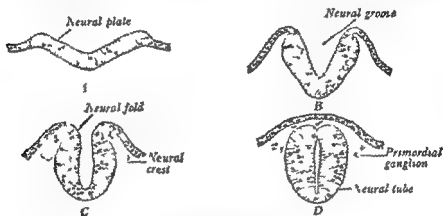


Fig. 389.—The development of the neural tube from the ectoderm (From Arcey, *Developmental Anatomy*, W. B. Saunders Co., Philadelphia.)

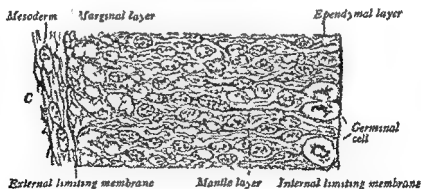


Fig. 390.—The cellular development of the neural tube (After Hildebrand, *Functional Development of the Nervous System*, W. B. Saunders Co., Philadelphia.)

creases in complexity and ascends in the scale of evolution newer functions come to be located in the anterior end of the neural tube the growth of which becomes much more rapid and is complicated by the formation of flexures (Fig. 371). It is from this increased growth and differentiation at the head end and the allocation of newer functions to this region that the brain is formed. The remainder of the neural tube retains much more its original conformation and becomes the spinal cord. The lumen of the tube persists as the central canal of the cord and the ventricles of the brain.

The structural and functional unit of nerve tissue is the neurone which consists of the nerve cell and its processes (Fig. 372). The cells vary in size

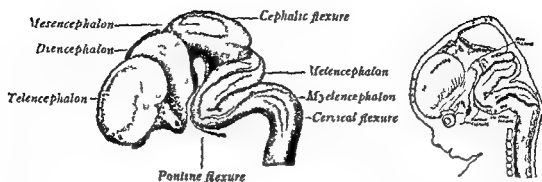


Fig. 371.—The development of the brain by the increased growth and differentiation and the formation of flexures at the head end of the neural tube (After Ellis From Gray's Developmental Anatomy W. B. Saunders Co Philadelphia)

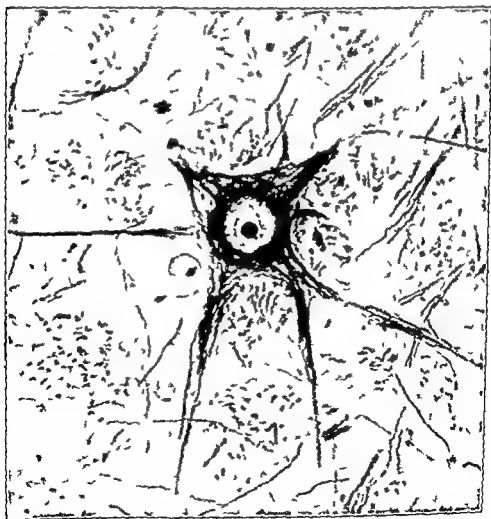


Fig. 372.—A nerve cell and its processes and the degree of magnification. The fine structure is not in focus because of its size. The neuron is clearly shown.

and shape from the small granular cells of  $4\ \mu$  to  $6\ \mu$  to the large Betz pyramidal cells, in the motor or pre Rolandic cortex, which may measure  $100\ \mu$  or more in their largest diameter. The processes are the dendrites, through which the cell receives impulses from other cells and the axone, which may be several feet in length and which is the efferent process of the cell. The individual axones are the nerve fibers which when grouped together form nerve tracts and peripheral nerves. Most of the axones in the nervous system do

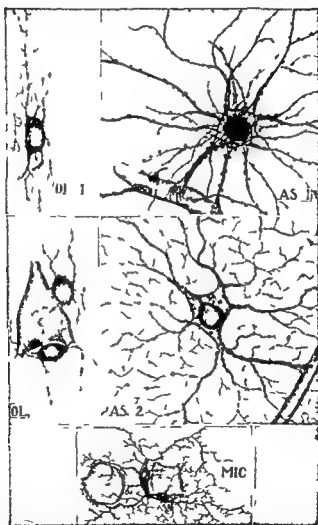


Fig. 373.—The histological cells of the central nervous system. OL, and OL 1, oligodendrocytes from man; the fibrous astrocyte, AS 1, fibrous astrocyte with perivascular foot plate; AS 2, protoplasmic astrocyte; MIC, microglia cell in relation to two nerve cells. (From Penfield, *Special Cytology*, edited by L. V. Cowley, Paul B. H. Eber, Inc., New York.)

not become functionally mature until they are myelinated. Myelin is a lipid material which covers the axone as insulating material covers a wire. It is formed during the latter part of intrauterine life and for several months after birth. In its deposition it follows functional pathways and ordinarily sensory fibers and tracts are myelinated before motor ones.

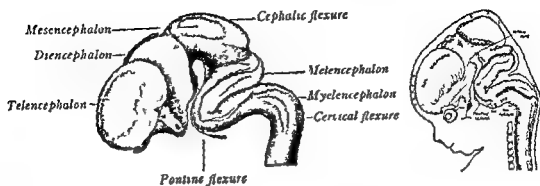


Fig. 371—The development of the brain by the increased growth and differentiation, and the formation of flexures at the head end of the neural tube. (After His From Vrey Developmental Anatomy W. B. Saunders Co Philadelphia)

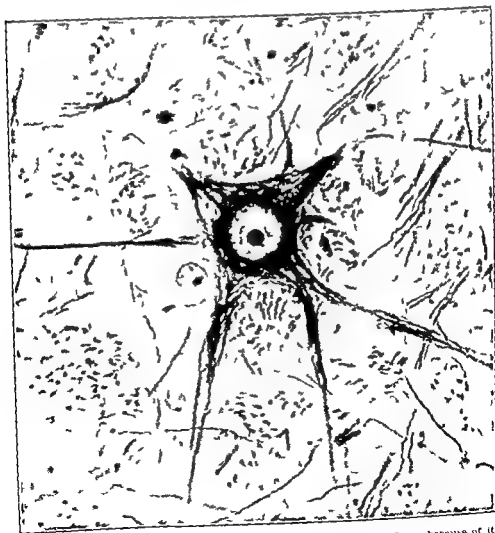


Fig. 37 —A nerve cell and its processes and the degree of magnification. The entire structure is not in focus because of it is too large. The neurofibrillar structure is clearly shown.

and shape from the small granular cells of  $\frac{1}{2} \mu$  to  $6 \mu$  to the large Betz pyramidal cells, in the motor or pre Rolandic cortex, which may measure  $100 \mu$  or more in their largest diameter. The processes are the dendrites, through which the cell receives impulses from other cells and the axone, which may be several feet in length and which is the efferent process of the cell. The individual axones are the nerve fibers which when grouped together form nerve tracts and peripheral nerves. Most of the axones in the nervous system do

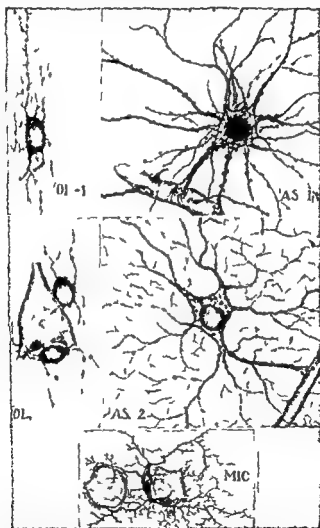


Fig. 373.—Types of cells of the central nervous system. OL and OL 1 oligodendrocytes from rat brain; AS 1 and AS 2 astrocytes from rat brain; MIC microglia from rat brain; OL 1 oligodendrocyte from rat brain; AS 1 and AS 2 astrocytes from rat brain; MIC microglia from rat brain. (From P. H. Field, "Spinal Cytology," edited by J. V. Cowdry, Paul B. Hoeber Inc. New York.)

not become functionally mature until they are myelinated. Myelin is a lipid material which covers the axone as insulating material covers a wire. It is formed during the latter part of intrauterine life and for several months after birth. In its deposition it follows functional pathways and ordinarily sensory fibers and tracts are myelinated before motor ones.

In fixed and stained nerve cells chromophilic Nissl granules are seen and these undergo changes, which are described later, in pathological processes. In the area about the origin of the axone and in the axone itself these granules are absent, although they are present in the dendritic processes. Nerve cells also contain neurofibrils, which can be shown by appropriate stains and can be followed into and through the course of the axone.

The interstitial cells of the nervous system are the neuroglia and microglia cells (Fig. 373). The neuroglia cells are developed from the ectoderm and consist of the astrocytes and oligodendroglia cells or oligodendrocytes. The microglia cells are of mesodermal origin. Astrocytes are either fibrous or protoplasmic (nonfibrous). The former occur in the white matter of the central nervous system, the latter in the grey matter. These large stellate cells invariably have one of their processes attached to a mesodermal structure, either a blood vessel or the pia, and this process or expansion is known as the perivascular or pial foot. The oligodendrocyte is a small cell with a darkly staining nucleus, little cytoplasm and fewer expansions than the astrocyte. It appears characteristically closely applied to nerve cells, as perineuronal satellites, and also in long parallel rows in the white matter between the myelinated axones. It is believed to have a secretory function concerned with the formation of myelin and it has no perivascular or pial foot such as that of the astrocyte. The mesodermal microglia cells have elongated or triangular nuclei and granular expansions which are characterized by short spines at right angles to the expansion itself. In pathological conditions microglia undergo profound changes and become phagocytic, a process which is described later.

The nervous system is made up of grey matter and white matter. The former consists of nerve cells, the latter of nerve fibers. In the brain (Fig. 374) the grey matter is located on the surface (cerebral cortex) and also in large nuclear masses within the brain, the basal ganglia, red nucleus etc. In the spinal cord (Fig. 375) the grey matter is inside and the white matter on the surface. Neuroglia and microglia cells are present in both grey and white matter.

For purposes of description the brain is divided into (1) telencephalon or forebrain, which is divided by the longitudinal fissure into two cerebral hemispheres; (2) diencephalon or between brain containing the thalamus and the hypothalamic nuclei; (3) the mesencephalon or midbrain including the corpora quadrigemina, red nucleus, substantia nigra and various cranial nerve nuclei; (4) the metencephalon or pons and cerebellum; and (5) the myelencephalon or medulla oblongata which is continuous with the spinal cord.

The surface of the brain in lower mammals, such as the rabbit, is smooth but as it ascends in the mammalian scale the surface becomes increasingly complex. In the human being (Fig. 376 and Fig. 377) it is formed into convolutions or gyri separated by fissures and sulci. In this way a greater surface, and so a greater number of nerve cells, can exist in any given area. Each of the convolutions separated by the sulci has its own name and in addition the fissures divide the brain up into larger subdivisions known as lobes.

The Rolandic or central fissure separates the frontal lobe from the parietal lobe the Sylvian fissure separates the temporal lobe below from the parietal and frontal lobes above and the parietooccipital fissure which is less well defined than the others separates the occipital lobe behind from the parietal and temporal lobes in front. In addition to these gross subdivisions, the cerebral cortex has been divided into a number of distinctive areas based upon



Fig. 34.—Sagittal section of the brain to show the gray matter on the surface and in the nuclei and masses in the interior white matter and cerebellum.

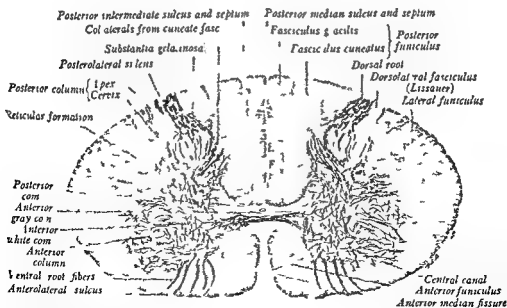


Fig. 35.—Diagram of a section through the brainstem and spinal cord of a child (taken by L. A. W. in 1911). This method stains the myelin sheaths alone. Tracts of white matter which have been stained are arranged around the grey matter. The grey matter contains but few fibers and its nerve cells are not shown because of the selective staining (for details see The Anatomy of the Nervous System W. H. Saunders Company Philadelphia 1911).

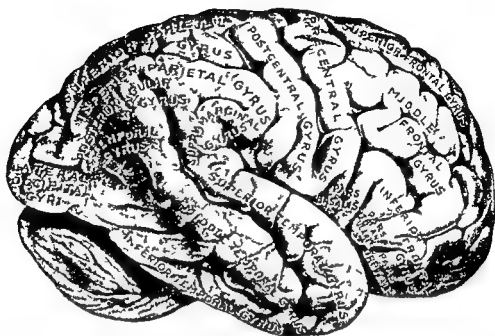


Fig 316—Brain viewed from the right (From Tinney and Riley, *The Form and Functions of the Central Nervous System* Paul B Hoeber New York 1923)

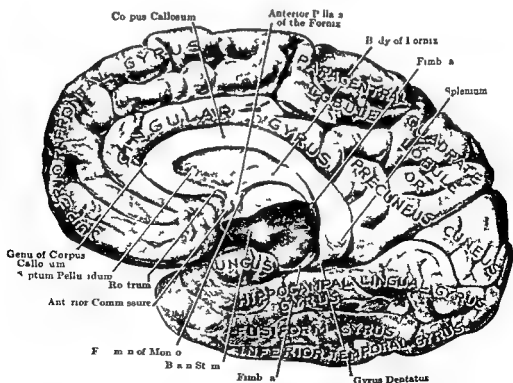


Fig 317—Right cerebral hemisphere viewed from the left (From Tinney and Riley, *The Form and Functions of the Central Nervous System* Paul B Hoeber New York 1923)



the architectural arrangement of the cells which form it. Brodman has differentiated 52 areas which differ in the distribution and type of cells occurring in the six layers which form the cortex.

The entire central nervous system is enveloped in three coverings which form the meninges. The outermost of these is the thick tough fibrous covering known as the dura mater or pachymeninges. Reflections of this penetrate the longitudinal fissure as the falx cerebri and also between the inferior surface of the cerebrum and the superior surface of the cerebellum as the tentorium. The tentorium divides the intracranial cavity into two parts, the

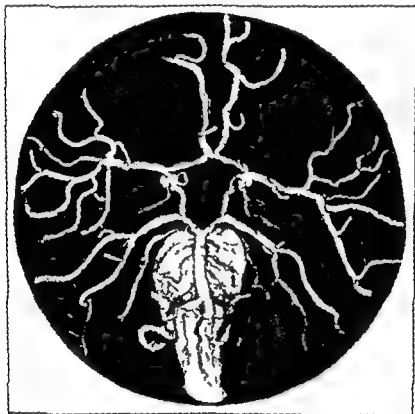


Fig. 318.—The circle of Willis. The cerebral arteries are on the ventral surface of the midulla and unite to form the basilar artery on the ventral surface of the pons. The internal carotid arteries have been cut and their lumina can be seen arising from the circle are the anterior, middle, and posterior cerebral arteries. In this particular illustration small symmetrical aneurysms can be seen just proximal to the bifurcation of the anterior and middle cerebral arteries. (Courtesy of Dr. W. H. Chase.)

supratentorial containing the cerebrum and the subtentorial containing the cerebellum and brain stem. Between the dura and the brain are the arachnoid and the pia mater which together form the leptomeninges. These can be imperfectly separated from one another as trabeculae join them. The arachnoid does not dip into the sulci while the pia does. In addition the pia mater penetrates into the brain substance with the blood vessels about which it forms the perivascular or Virchow Robin spaces.

The arterial blood supply to the brain is furnished by means of the internal carotid and the vertebral arteries. The internal carotid arteries reach

the intracranial cavity through the carotid canals and the vertebrals through the foramen magnum. At the base of the brain these arteries form the circle of Willis which gives off the anterior, middle, and posterior cerebral arteries (Fig. 378). The cerebellum and pons are supplied by branches of the basilar artery formed by the union of the two vertebral arteries. The venous blood is distributed to large sinuses in the folds of the dura and thence to the internal jugular veins which leave the skull through the jugular foramina. The blood supply to the spinal cord is derived from the vertebral and intercostal arteries. These form the anterior spinal and the posterior median arteries, which lie in the anterior median fissure, and give off branches to the anterior horns and for a variable distance beyond these. In addition the posterior spinal arteries form branches which extend around the periphery of the cord and send terminals in at right angles to its surface.

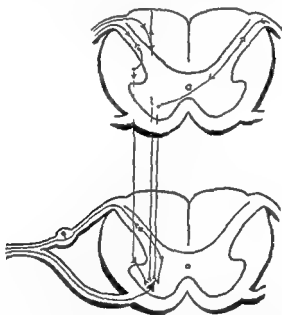


Fig. 39.—Diagram of a simple segmental reflex arc in lateral and uprasgmental reflexes showing how a ventral afferent pathway converges on one anterior horn cell and how spinal reflexes of different complexities may be brought about. (From Grinker, *Neurology*, Courtesy of Charles C. Thomas, Publisher, Springfield, Ill.)

The central nervous system regulates the adaptation of the individual to the environment, both external and internal. It is not alone in this regulation as the endocrine glands partake in the same function and there is an intimate correlation between nervous and hormone action. The adaptation may be a simple one such as the withdrawal of a limb from a noxious stimulus or a very complicated one such as the adjustment of the personality to an emotional situation. Mechanically this adaptation is brought about through the exercise of the properties of nervous tissue irritability and conductivity. Nervous tissue can be stimulated and can transmit the stimulus to a distance. Transmission of the nervous impulse along the axones, although accompanied by electrical change, is not transmission of an electrical current but the analogy to an electrical current is a useful one.

The simplest type of nervous action is the spontaneous discharges of energy which are shown by the wavelike change in action potential of nerve cells and fibers while at rest. The simplest form of exteriorization of nervous function is manifested by the simple reflex. Such a reflex forms an arc (Fig 379) which is made up of an afferent impulse ordinarily a sensory impulse coming into the central nervous system from the periphery and an efferent impulse usually a motor impulse going out from the central nervous system to the periphery. In between the afferent and the efferent neurones there is a third an intercalated neurone. The knee jerk is an example of such a reflex. A tap on the patellar tendon gives rise to an impulse which travels into the spinal cord through the posterior nerve root thence to the anterior horn cells and to the periphery through their axones. The result is a contraction of the quadriceps muscle of the same side and a rapid twitchlike extension of the leg at the knee joint. Reflexes may vary in complexity from the theoretically possible one involving one segment of the spinal cord to the highly complicated conditioned reflexes, such as the secretion of gastric juice in response to a stimulus which has previously been associated with the giving of food. It is possible that a great many personality reactions are built up on such a foundation of reflex action (see Chapter XVI).

### THE DIAGNOSIS OF NERVOUS DISEASES

The diagnosis of nervous diseases involves the determination of the site of the lesion and the nature of the lesion. These two problems the anatomical and the pathological necessitate careful history taking careful physical examination and the careful and judicious use of the special examinations which are available.

The anatomical diagnosis of nervous diseases or the determination of the site of the lesion depends almost entirely on physical examination. Abnormal physical signs depend upon the part that is involved and not upon the type of lesion. Thus a destructive lesion of the pyramidal tract whether vascular inflammatory neoplastic or other will produce an upper motor neurone type of paralysis in the part supplied by the destroyed fibers.

Lesions of the nervous system may be irritative as in epileptic discharges and fibrillary movements or destructive as in motor paralyses and sensory losses. Because of the integrating character of the nervous system and the correlation of its different parts to one another a destructive lesion will do two things (1) it will abolish the function of the part it has destroyed, giving rise to paralytic phenomena and (2) it will release the remainder of the central nervous system from the inhibitory or modifying influences ordinarily exerted by the destroyed part and so will give rise to release phenomena. These two types of physical signs are well shown in lesions of the pyramidal tract.

The remainder of this section is devoted to the consideration of the anatomical diagnosis of nervous diseases and pathological considerations are dealt with in the following section.

### Disturbances of Motility

Voluntary motion is a complex function which is controlled by many areas of the central nervous system. It is exteriorized through the pyramidal (cortico spinal) tract or upper motor neurones, and through the anterior horn cells and their axones or the lower motor neurones. In addition, however for its useful functioning it requires to be coordinated, a function which is controlled by the cerebellum. Control and maintenance of posture and of tonus are also necessary and these are made possible through the integrity of vestibular reflexes, striatal pathways and of impulses which are exteriorized through the rubrospinal and reticulospinal tracts. Ordinarily in dealing with impairment of motor function one speaks of paralysis of muscles and yet this term is usually misapplied. In upper motor neurone lesions for example, there is a paralysis of voluntary movement but by no means a paralysis of muscles, the reflex excitability of which may be increased.

It has been said that the exteriorization of voluntary movement is brought about through the action of two neurones, the upper motor neurone and the lower motor neurone. Because of this there are two types of lesions the physical manifestations of which are shown in the following comparative tabulation.

	UPPER MOTOR NEURONE LESION	LOWER MOTOR NEURONE LESION
Nutrition	Preserved no atrophy except that of disuse	Impaired atrophy is present
Power	Diminished or lost	Diminished or lost
Tonus	Increased	Diminished
Clonus	Present	Absent
Tendon reflexes	Increased	Diminished or lost
Superficial reflexes	Abolished	Abolished
Pathological reflexes	Present	Absent
Faradic excitability	Preserved	Diminished or absent

In muscles which are undergoing atrophy due to lesions of the anterior horn cells and which are not yet fully paralyzed fibrillary movements are frequently and characteristically observed. Similar fibrillations may occur with disease elsewhere in the lower motor neurone. The increase in tonicity or resistance to purely passive movements in upper motor neurone lesions is usually more marked in the flexor groups of muscles. Frequently at the onset of hemiplegia resulting from a lesion of the pyramidal tract tonicity will be diminished in the parts involved and the tendon reflexes will be absent but usually within forty-eight hours this state will begin to pass into that characteristic of a pyramidal tract lesion. The cause of the diminution in tone and absence of tendon reflexes in such a case is the widespread and sudden shock to which the entire central nervous system is subjected. On the other hand there are cases of hemiplegia in which the diminution in tonicity remains. At the present time it is believed that if components of the pyramidal tract arising from both area 6 and area 4 (Brodmann) of the cerebral cortex are involved, the hemiplegia will be spastic whereas if only area 6 or its axones is involved the hemiplegia will be flaccid. The chief superficial reflexes that are tested are the abdominal and plantar reflexes. The normal response to stroking lightly the outer border of the sole of the foot is flexion of all the toes but in

pyramidal tract lesions, or upper motor neurone lesions, a pathological reflex replaces this normal one. In such cases stimulation produces extension of the big toe with or without flexion and fanning of the remaining toes (plantar extensor response or Babinski sign). This same response can be brought about and so corroborated, by other types of stimulation such as stroking the outer border of the foot (Chaddock reflex) or by forcibly running the fingers along the borders of the tibia (Oppenheim reflex). Other pathological reflexes occur which are less dependable and the presence of which cannot with certainty point to the particular location of the lesion within the central nervous system. Faradic excitability of a nerve muscle preparation depends upon the integrity of the myoneural junction and in lower motor neurone lesions, after a sufficient interval (10 to 20 days) has elapsed for the axone to degenerate, this excitability is lost. Galvanic excitability on the other hand is exerted directly on the muscle fibers and as long as these remain contractile it is preserved although it is altered in lower motor neurone lesions.

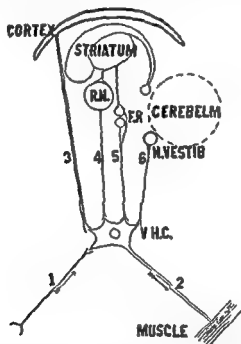


Fig. 280.—Diagram of the final common path and the various levels of the nervous system acting upon it. R.V. = red nucleus; P.P. = formatio reticularis; V.H.C. = ventral horn cell; S. = simple reflex; C. = the final common path; S. = the cortico-pyramidal or pyramidal tract; J. = the rubro-pyramidal tract; R. = the reticulo-pyramidal tract; 6 = the cerebro-pyramidal tract. (From Lennox and Cobb. Epilepsy. Williams and Wilkins Company, Baltimore.)

In further considering the physical manifestations outlined in the above table several striking features are noted. In the first place a lower motor neurone lesion diminishes or abolishes all of the functions recorded. On the other hand in upper motor neurone lesions some functions are diminished or lost (power superficial reflexes) some are preserved (nutrition faradic excitability), some are increased (tonus tendon reflexes) and some new things make their appearance (pathological reflexes clonus). This is easy to understand when one recalls that the lower motor neurone is the final common

pathway of transmission of motility and its correlated phenomena to the periphery and so a lesion of this final common pathway will prevent the exteriorization of all the modalities of function which are transmitted to the anterior horn cells and conducted along their axones (Fig. 380). The upper motor neurone, however, is not a final common path. Its impulses are exerted on the anterior horn cell which receives in addition impulses from many other pathways, such as the rubrospinal, reticulospinal and vestibulospinal tracts and also the pathways for reflex action which exist within the cord itself. As a result of this a lesion of the pyramidal tract will cause abolition of the function being transmitted along the pyramidal pathway but it will leave the lower motor neurone free to exteriorize functions being transmitted to it by other pathways. Furthermore these functions are no longer subjected to the inhibitory influences which the pyramidal tract normally places upon them and so may be increased or otherwise altered.

The anatomical diagnosis in cases of disturbance of motility depends not only on the determination of what pathway is involved but also upon where in its course it is involved. The pyramidal tract arises from the large pyramidal (Betz) cells in the pre-Rolandic area. The axones of these cells converge as they pass downward between the basal ganglia where they form the internal capsule and then descend into the medulla as compact and circumscribed bundles. As it passes through the midbrain, pons and medulla this tract gives off its cranial nerve components which cross to the cranial nerve nuclei of the opposite side. When the tract reaches the lower medulla it crosses almost completely and descends in the opposite side of the spinal cord. Those fibers which do not cross but descend the homolateral side of the cord do not concern us in a text of this kind. Having reached the segment of the cord which supplies the part to which they are conveying function the fibers synapse with the anterior horn cells or cells of the lower motor neurones. The axones of the latter which, as was noted above, are subjected to influences from several pathways, then transmit the impulse to the periphery. It is apparent therefore that the pyramidal tract arising in one hemisphere of the brain carries impulses to the opposite side of the body whereas the lower motor neurone arises from the same side of the cord as that of the body to which it is distributed. Furthermore the lower motor neurone is strictly a segmental structure, whereas the pyramidal tract is not. In the motor cortex the fibers which are to supply the leg arise uppermost, those for the arm and trunk are in the middle, and those for the face, tongue and jaw are at the lower end of the pre-Rolandic convolution.

In the accompanying diagram (Fig. 381) destructive lesions have been marked at different levels to indicate characteristic types of syndromes. As the consideration of irritative phenomena of the cerebral cortex is particularly applicable to the discussion of the cerebral cortex and of the epilepsies it has been reserved for those sections (pages 1006 *et seq.* and 1152).

Lesion 1 is located in the pre-Rolandic cortex and immediately subcortical. Because of its size it involves the fibers only to one limb and so will cause a monoplegia of the upper motor neurone type. If it is located high up

in the motor cortex, as illustrated, the paralysis will be in the leg, if it is situated lower down, about the middle of the motor area the paralysis will be in the arm, while if it is in the lowest part of the motor convolution the paralysis will be in the face and adjacent structures. In each case the paralysis will be contralateral, that is, on the opposite side of the body to that of the brain in which the lesion is located.

Lesion 2 is of approximately the same size, but is situated in the internal capsule where the corticospinal fibers have converged as they pass downward. Resulting from it there will be a hemiplegia of the opposite side of the body with an upper motor neurone type of paralysis of the face, arm and leg. Other cranial nerves such as the oculomotor and hypoglossal may also be involved.

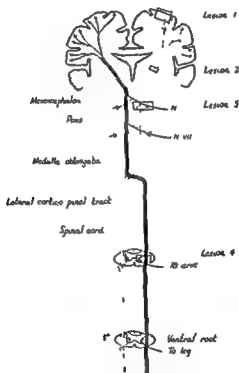


Fig. 351.—A diagrammatic representation of lesions at different levels in the upper and lower motor neurones. Resulting symptoms are described in the text. (Modified from Ranvier, *The Anatomy of the Nervous System*, W. B. Saunders Company.)

Lesion 3 explains anatomically the crossed paralysis in which a cranial nerve is paralyzed on the same side as the lesion and the arm and leg on the opposite side of the body. The various combinations have been given the names of the observers who first described them but the important thing is that each combination is due to a lesion situated at the level of origin of the cranial nerve involved on the same side. Thus a lesion on one side of the midbrain at the level of origin of the oculomotor nerve and involving it and the pyramidal tract will cause a homolateral oculomotor paralysis and a contralateral paralysis of arm and leg. Similarly a lesion in the pons will cause

a homolateral facial paralysis and a contralateral paralysis of arm and leg

Lesion 4 is in the cervicothoracic enlargement, made up of the segments of the cord supplying the upper extremity. The lesion involves the lower motor neurones to the arm and the upper motor neurones for the body segments below the arm. The result will be a flaccid, atrophic, lower motor neurone



Fig. 382.—The lumbosacral cord and cauda equina. (L. Berg. Am. J. M. Sc. Philadelphia 1911.)

type of paralysis in the arm, absent abdominal reflexes, and a spastic upper motor neurone paralysis of the leg with increased tendon jerks and plantar extension (Babinski sign) following stimulation of the sole of the foot. All the physical signs will be homolateral that is on the same side as the lesion because the pyramidal tract is involved in the cord after it has crossed in the



medulla. If the lesion is too small to involve all the lower motor neurones to the arm the flaccid paralysis will be confined to the distribution of those that are involved.

At birth the spinal cord fills the vertebral canal and each mixed nerve made up of anterior and posterior nerve roots passes horizontally through the intervertebral foramen at its own level. As growth progresses the vertebral column increases greatly in length whereas the spinal cord does not. The spinal nerves passing through the intervertebral foramina are consequently pulled out of their original position by the growing vertebral column and instead of passing horizontally out of the vertebral canal descend within the canal until they reach their own foramina. This descent is not present in the upper spinal nerves in the cervical region, because at that level the growth is not disproportionate but at progressively lower segments of the vertebral column the disproportion becomes progressively more marked and the segment of the cord no longer lies opposite its corresponding vertebra. In adult life the spinal cord ends opposite the first lumbar interspace and all the spinal nerves which are to leave through lower intervertebral foramina must descend below the termination of the cord. The mass of lumbar and sacral nerves which thus pass downward in the vertebral canal forms the cauda equina (Fig. 352) which contains both motor and sensory fibers. The motor fibers in the cauda equina are therefore all axones of anterior horn cells and so all lower motor neurone structures. Motor paralysis following cauda equina lesions are consequently of the lower motor neurone type.

Electrical stimulation of the precentral cortex produces focal movements of single muscles or of a very restricted number of muscles and not fully developed purposive action. It is obvious that higher centers of initiation and elaboration of combined muscle movement must exist within the brain centers which build the individual muscle components into the complex pattern which volition dictates. Very little is known of these centers. The frontal adhesive field situated in the posterior part of the first and second frontal convolutions is one such area and stimulation of this produces turning of head and eyes to the opposite side while destruction produces head and eye turning to the same side. Not only must all the components of complex purposive movements be set in action but their action must also be synergized or coordinated and this is accomplished through the action of the cerebellum.

The cerebellum has two hemispheres which are joined by the vermis. The cortex is made up of three layers of cells and within the cerebellum itself are several grey nuclear masses the largest of which is the dentate nucleus. Connection with the brain stem is made by three pairs of peduncles the superior or brachium conjunctivum the middle or brachium pontis and the inferior or corpus restiforme. Through the inferior cerebellar peduncle afferent impulses enter the cerebellum from the dorsal spinocerebellar tract the nuclei of Goll and Burdach the vestibular nucleus and the inferior olives. Through the middle cerebellar peduncle fibers from the opposite pontine nuclei enter. These are fibers of the corticopontocerebellar system from the cortex of the frontal and temporal lobes particularly. The superior cerebellar peduncle is an efferent structure made up chiefly of fibers from the dentate

nucleus of one cerebellar hemisphere to the opposite red nucleus and thalamus. From the red nucleus arises the rubrospinal tract which crosses at once and descends into the spinal cord. Efferent cerebellar impulses therefore cross from one cerebellar hemisphere to the opposite red nucleus and then, by means of the rubrospinal tract, back to the homolateral side of the spinal cord. Afferent fibers of the ventral spinocerebellar tract, from the homolateral side of the spinal cord, enter the cerebellum in close contact with the brachium conjunctivum. Consequently the connections of the cerebellum proximal to itself are chiefly with the opposite side of the brain and the connections distal to itself are chiefly with the same side of the cord.

Since the cerebellum is a coordinating center, destruction of it impairs coordination and leads to ataxia and dysnergia. The incoordination is manifested on the same side of the body as the side of the cerebellum involved, and can be tested for by having the patient carry out any movement which requires muscular coordination. Walshe has described the symptomatology as follows: (1) abnormalities of resting muscle—loss of tone, (2) abnormalities of muscular contraction—excessive range and force of contraction, intermittent and unsteady contraction, premature relaxation, extreme readiness of fatigue, (3) abnormalities of voluntary movements—faulty functional combination of the muscles engaged in a voluntary movement, (4) the effect of voluntary efforts at correction.

Clinically the following abnormal signs occur. There is nystagmus when the eyes look laterally toward the side of the lesion. Speech is ataxic, slurred and jerky. There is incoordination, especially in fine movements such as touching the nose with the finger, touching the finger of the examiner, rapid tapping of the finger on a table, rapid alternate pronation and supination of the forearm (dysdiadokokinesia), placing the heel of one foot on the opposite knee, etc. The ability to carry out movements accurately is lost, if the patient attempts to reach for an object he will overshoot the mark or fall short of it and his attempts to correct this will result in clumsy, inaccurate movements. There is also difficulty in stopping movements when they should be stopped, for example, if forcible flexion of the patient's forearm is prevented by the examiner's hand and if the latter is suddenly removed, the patient's forearm will not relax in time and will rebound forcibly. The gait is also disturbed and the patient tends to sway or stagger or fall toward the side of the lesion. In some cases in an effort to overcome this deviation from a straight line, the patient's body will turn slightly away from the side of the lesion while the head turns slightly toward the side of the lesion. Tremor frequently occurs and it is a tremor which becomes coarser and more marked on voluntary movements ('intention' tremor) or may be present only at such times. As noted in Walshe's description of the symptomatology there is usually some diminution in muscle tonus on the side of the lesion and some times because of the impairment described above, voluntary power will be slightly diminished. With these changes the knee jerk sometimes becomes pendular in type and the unsupported leg will swing backward and forward after the knee jerk has been elicited.

The maintenance of tone depends upon the integrity of the segmental reflex arcs, and for that reason when the lower motor neurone, or the efferent pathway of the arc, is destroyed, tonicity is abolished. In addition, however, higher centers modify the degree and distribution of the tonus. It has been stated that in pyramidal tract lesions tonicity is increased and this increase is primarily a flexor increase in the arm. In cerebellar disease tonicity is diminished. In disease of the extrapyramidal motor system the striatal, rubral and reticular pathways, tonicity is also increased, but the increase is general and not selective as that of the pyramidal cases. Furthermore in extrapyramidal disease, increased tonicity is of the "cog wheel" character, and passive movement of the limb reveals not a constant increase in tone but a succession of hypertonicity and relaxation.

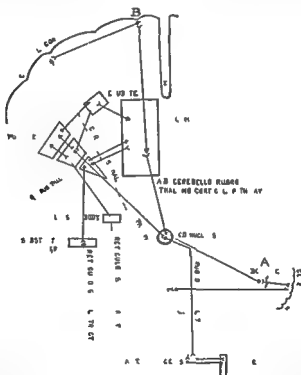


Fig. 383—A diagrammatic representation of the extrapyramidal pathways. (From Young, M. J. 1934.)

The maintenance of posture and the righting reflexes of the body are subserved by mechanisms associated with extrapyramidal pathways and with reflexes set in action by afferent impulses arising from the eyes, body, neck and labyrinth. Exteriorization of function is brought about by vestibulospinal, rubrospinal and reticulospinal pathways. The discussion of decerebrate rigidity, and of paraplegia in flexion and in extension is postponed until the end of this section.

The extrapyramidal pathways are efferent systems of the corpus striatum, the red nucleus, the reticular nuclei and the vestibular nucleus of Deter. The last forms a vestibulospinal tract concerned with reflex responses to stim-

ulation of the semicircular canals by changes in posture of the head. The remainder of these pathways are represented in Fig. 383. It will be seen from this that the systems are largely split up into relays and that they exteriorize function arising in the basal ganglia, the cerebellum and various hypothalamic diencephalic and mesencephalic nuclei. The anatomical connections of these various paths have not yet been fully determined.

Disease of these extrapyramidal pathways results in disturbances of tone and the appearance of abnormal movements. The abnormal movements are tremors, chorea, athetosis and dystonic movements. While attempts have been made to explain each particular type of abnormal movement on disease of a particular nucleus of this system they are unwarranted at present. It is possible, and indeed likely, that the pathogenesis is based not upon disease of one nucleus or path only but of the complex connections between the cerebral hemispheres, cerebellum and extrapyramidal motor nuclei. Experimentally it has not been possible to reproduce these symptoms.

Choreic movements are rapid irregular hypotonic objectively purposeless but subjectively purposeful movements which may involve any part of the body. They may be confined to the face, one limb, one side or be generalized. They are separate, abrupt, irregular and of short duration. They may consist of fine movements such as of the fingers or tongue or of violent constant movements sufficient to throw the patient out of bed. Further characteristics are described in the section on Chorea (Chapter III). Athetosis like chorea may involve any part of the body and frequently occurs after infantile hemiplegia which has partially recovered. The movements are slower, more grotesque, and may be brought on by voluntary movement of the affected limb or the opposite one. They are frequently forcible extensor or flexor movements of hands or fingers, feet or toes associated with marked increase in muscular tone. Slow tortuous movements of the arms away from the body also occur. The movements of dystonia musculorum or torsion spasm resemble athetosis in many ways but are usually more widespread involving at first a whole segment of the body and perhaps later the entire body which is twisted forcibly into bizarre patterns. These movements are impossible to describe accurately, but once seen will not be forgotten. The tremor of extrapyramidal disease is unlike that which occurs in lesions of the cerebellum and its superior peduncle. In the former the tremor which may be of the 'pill rolling' variety is present at rest and usually disappears when voluntary movements are made while in the latter the tremor is induced or increased by voluntary movements, the so-called 'intention tremor'. At times it is difficult to separate these two types. All these movements are release phenomena and they are abolished if the upper or lower motor neurone is completely destroyed because their exteriorization is brought about through these systems.

### Somatic Sensibility

Somatic sensibility is conveyed to the central nervous system by sensory fibers which enter the cord through the posterior nerve roots. The cells of these fibers are situated in the posterior root ganglia which are outside the central nervous system itself and which have developed from the ectodermal

neural crest. Many types of cells have been described in these ganglia and the sensory fibers themselves have been subdivided according to whether or not they are myelinated and, if so according to how heavily myelinated they are. Not only do the fibers carrying different types of sensibility have different thicknesses of myelin covering them, but they also have different conduction rates. The types of sensibility entering the spinal cord from skeletal structures are touch, pain, position (muscle and joint sense) and vibration.

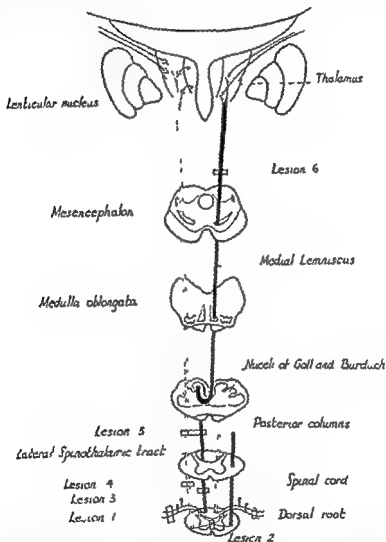


Fig. 384.—A diagrammatic representation of the sensory pathways. The fibers from one side of the body are in solid line and those from the other side in broken line. Lesions have been marked in at different levels and are explained in the text. (Modified from Panson, *Anatomy of the Nervous System*, W. B. Saunders Company.)

After entering the cord the fibers carrying position and vibration sensibility ascend the homolateral columns of Goll and Burdach (posterior columns) to the medulla where they enter the nuclei of Goll and Burdach. New neurones there pick up the function and their axones cross to the medial lemniscus of the opposite side and terminate in the ventral nucleus of the thalamus. Some

of the fibers from the nuclei of Goll and Burdach terminate in other nuclear structures in the midbrain and diencephalon, but these connections have not been fully established

The fibers conveying pain and temperature sensibility end in the grey matter immediately on entering the cord. New fibers then convey function across the midline, anterior to the central canal of the cord, to the opposite spinothalamic tract. The crossing takes place at the level at which the corresponding fibers have entered the cord or within one or two segments above that. The fibers of the spinothalamic tract ascend in the cord and brain stem and also terminate in the ventral nucleus of the thalamus. Many of the fibers of the spinothalamic tract terminate before reaching the thalamus, but again the anatomical details of these are obscure. Within the thalamus there are intimate connections between the various nuclei, and from the thalamus sensation is conveyed to the cerebral cortex by fibers which pass through the internal capsule posterior to the descending pyramidal tract fibers. Most of these corticospinal axones terminate in the post Rolandic convolution but some go to the pre Rolandic convolution and others to the parietal cortex. Touch sensibility is transmitted upward by both spinothalamic and posterior column systems. Consequently sensation from each half of the body ascends in both sides of the spinal cord but eventually all sensation which is to reach consciousness from one half of the body is distributed to the opposite cerebral hemisphere.

From a knowledge of these anatomical details one can determine the location of lesions which produce sensory disturbances in the periphery (Fig 384). In the first place, a lesion in a segmental structure the nerve root or the crossing fiber to the spinothalamic tract, will produce signs within the segmental distribution only whereas a lesion of the posterior columns or spinothalamic tract will produce sensory disturbances at all levels below the lesion as these tracts are transmitting sensation from all the segments. Second the type of sensory impairment will depend upon the fibers involved. Again a diagrammatic representation of lesions is used in explanation.

Lesion 1 is in the peripheral nerve or the posterior nerve root and the sensory loss resulting will involve all forms of somatic sensibility in the segmental distribution of the fibers involved. The segmental distribution of the posterior nerve roots and spinal cord segments is discussed later.

Lesion 2 is in the commissural fibers, carrying pain and temperature sensibility from one posterior grey horn to the opposite spinothalamic tract so the sensory loss will again be of segmental distribution. From the foregoing explanation the anesthesia should be for pain and temperature sensibility but clinically a dissociation of these two types of sensibility may be found for example temperature sensibility may be lost and pain sensibility preserved as so often happens in typical syringomyelia.

Lesion 3 is in the posterior columns of one side and will abolish vibration and position sense and two point discrimination on the same side of the body up to the level of the lesion. The patient will not be able to perceive or ap

perceive passive changes in the position of muscles and joints in the involved area nor the vibration of a tuning fork placed over a bony point in that area. In addition it will require a wider separation than normal of two points in order that they may be appreciated as two rather than as one. Of course as in all neurological conditions function may not be completely abolished but only reduced if the destruction of the pathway is not complete.

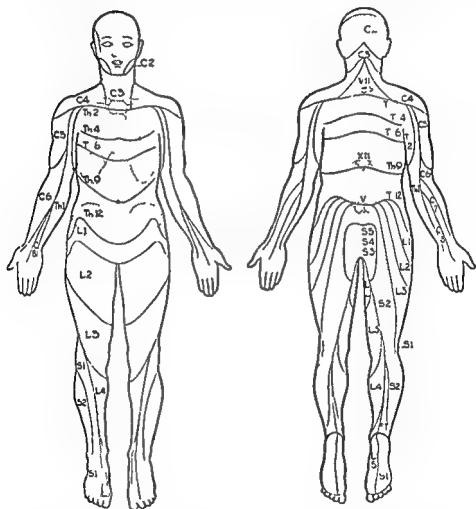


Fig. 38.—Diagrams to show the segmental distribution of the spinal cord segments and nerve roots (Lisberg).

Lesion 4 is in the spinothalamic tract on one side and will abolish pain and temperature sensibility on the opposite side of the body up to the level of the lesion. Because of the fact that fibers to the spinothalamic tract from progressively higher levels push those from lower levels toward the periphery of the cord it sometimes happens that in intramedullary lesions or lesions within the spinal cord which cause a loss of pain and temperature sensibility up to the level of the lesion sensory fibers from the distribution of the sacral segments will escape and sensation which they are transmitting will be preserved.

of the fibers from the nuclei of Goll and Burdach terminate in other nuclear structures in the midbrain and diencephalon, but these connections have not been fully established

The fibers conveying pain and temperature sensibility end in the grey matter immediately on entering the cord. New fibers then convey function across the midline, anterior to the central canal of the cord, to the opposite spinothalamic tract. The crossing takes place at the level at which the corresponding fibers have entered the cord or within one or two segments above that. The fibers of the spinothalamic tract ascend in the cord and brain stem and also terminate in the ventral nucleus of the thalamus. Many of the fibers of the spinothalamic tract terminate before reaching the thalamus, but again the anatomical details of these are obscure. Within the thalamus there are intimate connections between the various nuclei, and from the thalamus sensation is conveyed to the cerebral cortex by fibers which pass through the internal capsule posterior to the descending pyramidal tract fibers. Most of these corticospinal axones terminate in the post Rolandic convolution but some go to the pre Rolandic convolution and others to the parietal cortex. Touch sensibility is transmitted upward by both spinothalamic and posterior column systems. Consequently sensation from each half of the body ascends in both sides of the spinal cord but eventually all sensation which is to reach consciousness from one half of the body is distributed to the opposite cerebral hemisphere.

From a knowledge of these anatomical details one can determine the location of lesions which produce sensory disturbances in the periphery (Fig 394). In the first place a lesion in a segmental structure the nerve root or the crossing fiber to the spinothalamic tract, will produce signs within the segmental distribution only whereas a lesion of the posterior columns or spinothalamic tract will produce sensory disturbances at all levels below the lesion as these tracts are transmitting sensation from all the segments. Second the type of sensory impairment will depend upon the fibers involved. Again a diagrammatic representation of lesions is used in explanation.

Lesion 1 is in the peripheral nerve or the posterior nerve root and the sensory loss resulting will involve all forms of somatic sensibility in the segmental distribution of the fibers involved. The segmental distribution of the posterior nerve roots and spinal cord segments is discussed later.

Lesion 2 is in the commissural fibers carrying pain and temperature sensibility from one posterior grey horn to the opposite spinothalamic tract, so the sensory loss will again be of segmental distribution. From the foregoing explanation the anesthesia should be for pain and temperature sensibility but clinically a dissociation of these two types of sensibility may be found, for example, temperature sensibility may be lost and pain sensibility preserved as so often happens in typical syringomyelia.

Lesion 3 is in the posterior columns of one side and will abolish vibration and position sense and two point discrimination on the same side of the body up to the level of the lesion. The patient will not be able to perceive or ap



becomes hyperemic, its edges become blurred and swollen the veins become turgid and tortuous and exudate may obliterate some of the vessels. The degree of swelling may be measured by means of the lenses on the ophthalmoscope and so the progress or recession of the swelling can be accurately followed. After a long continued swelling of this type the nerve may undergo secondary atrophy, the exudate organizes, the disc becomes greyish white in color the vascular supply diminishes and the margins remain indistinct.

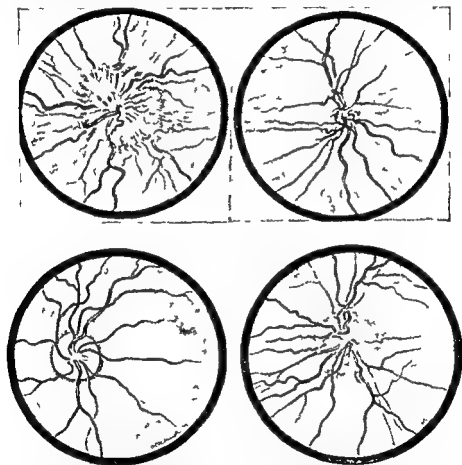


Fig. 386.—Above on the right a beginning choked disc on the left a highly choked disc with hemorrhage. Below on the right secondary optic atrophy on the left primary optic atrophy. (From Cr. Ker. Neurology. Courtesy of Charles C. Thomas, Publisher, Springfield, Ill.)

In contradistinction to secondary optic atrophy following papilledema due to increased intracranial pressure primary optic atrophy follows direct involvement of the nerve in disease particularly in tumors, tabes dorsalis and disseminated sclerosis. In primary atrophy the disc becomes white, the margins are very sharply delimited and the vascularity diminishes. In addition to swelling and atrophy of the disc the retina may show characteristic changes in arteriosclerosis, diabetes, nephritis, military tuberculosis and hemorrhagic diseases so that the value of ophthalmoscopy is not confined to the diagnosis of nervous diseases.

Lesion 5 is a combination of the last two and involves the spinothalamic tract and the posterior columns on the same side of the cord. This will result in a homolateral loss of position and vibration sensibility and a contralateral loss of pain and temperature sensibility both up to the level of the lesion.

Lesion 6 involves the medial lemniscus of one side and so interrupts fibers from the opposite nuclei of Goll and Burdach. The result will be a loss of position and vibration sense on the opposite side of the body.

The segmental distribution of the spinal cord is represented in Fig. 385. The diagrams compiled by different observers vary but little and agree in most details. It will be seen that the lowest segmental distribution, that of the third, fourth, and fifth sacral segments and roots, supplies a saddle shaped area around the anus and the genitals and perineum. The second sacral supplies a narrow strip up the back of the leg; the first lumbar supplies the region of Poupart's ligament; the seventh thoracic or dorsal segment supplies the level of the xiphisternum. Although the representation over the limbs, especially the legs, may not appear to be segmental, it is truly segmental from a developmental standpoint, as the limb buds, which have pulled out their nerve supply with them, undergo some rotation. It will be noted from the chart that if sensation is lost on the body up to the level of the second rib, it is necessary then to examine the segments distributed to the arms and hands to determine whether or not higher segments are involved. The accurate localization of lesions involving the spinal cord depends upon a knowledge of the pathways that are involved and also upon the segmental distribution as illustrated in the figure, so that the level of involvement may be determined.

### The Cranial Nerves

The cranial nerves are twelve in number on each side. They are either motor or sensory or mixed, and they pass from the base of the brain through foramina in the skull to and from the parts which they innervate.

The first or olfactory nerve carries sense of smell from the mucous membrane of the nose where the fine filaments to the olfactory bulb arise. Impairment of sense of smell is usually due to local causes in the nose, but in the case of tumors on the ventral surface of the frontal lobe in the olfactory groove anosmia may occur and may be a localizing sign of value. Hallucinations of smell are sometimes present in temporal lobe tumors as a result of irritation of the olfactory cortex in the uncinate gyrus. This usually occurs as a paroxysmal discharge which is part of a focal epileptic attack and is often associated with other phenomena especially auditory or visual. The hallucination is most frequently a disagreeable one.

The second cranial nerve or the optic nerve is the special sensory nerve from the retina. Testing of its function forms one of the most important parts of a neurological examination and may show signs of extreme value from the standpoint of both anatomical and pathological diagnosis. In the first place the fibers of this nerve can be seen on ophthalmoscopic examination, and when intracranial pressure becomes increased the nerve head or optic disc becomes visibly swollen and edematous. Normally this optic disc (Fig. 386) is a sharply outlined yellowish white circular area, but when swollen it

becomes hyperemic, its edges become blurred and swollen the veins become turgid and tortuous and exudate may obliterate some of the vessels. The degree of swelling may be measured by means of the lenses on the ophthalmoscope and so the progress or recession of the swelling can be accurately followed. After a long continued swelling of this type the nerve may undergo secondary atrophy, the exudate organizes, the disc becomes greyish white in color the vascular supply diminishes and the margins remain indistinct.

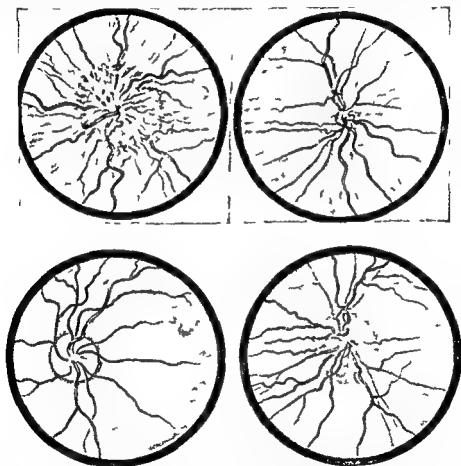


Fig. 388.—Above on the right a beginning choked disc on the left, a highly choked disc with hemorrhage. Below on the right secondary optic atrophy on the left, primary optic atrophy. (From Grinker's "Neurology," Court 3 of Charles C. Thomas, Publisher, Springfield, Ill.)

In contradistinction to secondary optic atrophy following papilledema due to increased intracranial pressure primary optic atrophy follows direct involvement of the nerve in disease particularly in tumors, tabes dorsalis and disseminated sclerosis. In primary atrophy the disc becomes white the margins are very sharply delimited and the vascularity diminishes. In addition to swelling and atrophy of the disc the retina may show characteristic changes in arteriosclerosis, diabetes, nephritis, military tuberculosis and hemorrhagic diseases so that the value of ophthalmoscopy is not confined to the diagnosis of nervous diseases.

Lesion 5 is a combination of the last two and involves the spinothalamic tract and the posterior columns on the same side of the cord. This will result in a *homolateral* loss of position and vibration sensibility and a *contralateral* loss of pain and temperature sensibility both up to the level of the lesion.

Lesion 6 involves the medial lemniscus of one side and so interrupts fibers from the opposite nuclei of Goll and Burdach. The result will be a loss of position and vibration sense on the opposite side of the body.

The segmental distribution of the spinal cord is represented in Fig. 385. The diagrams compiled by different observers vary but little and agree in most details. It will be seen that the lowest segmental distribution, that of the third, fourth, and fifth sacral segments and roots, supplies a saddle shaped area around the anus and the genitals and perineum. The second sacral supplies a narrow strip up the back of the leg, the first lumbar supplies the region of Poupart's ligament, the seventh thoracic or dorsal segment supplies the level of the xiphisternum. Although the representation over the limbs, especially the legs, may not appear to be segmental, it is truly segmental from a developmental standpoint as the limb buds, which have pulled out their nerve supply with them, undergo some rotation. It will be noted from the chart that if sensation is lost on the body up to the level of the second rib, it is necessary then to examine the segments distributed to the arms and hands to determine whether or not higher segments are involved. The accurate localization of lesions involving the spinal cord depends upon a knowledge of the pathways that are involved and also upon the segmental distribution as illustrated in the figure so that the level of involvement may be determined.

### The Cranial Nerves

The cranial nerves are twelve in number on each side. They are either motor or sensory or mixed and they pass from the base of the brain through foramina in the skull to and from the parts which they innervate.

The first, or olfactory nerve carries sense of smell from the mucous membrane of the nose where the fine filaments to the olfactory bulb arise. Impairment of sense of smell is usually due to local causes in the nose, but in the case of tumors on the ventral surface of the frontal lobe, in the olfactory groove anosmia may occur and may be a localizing sign of value. Hallucinations of smell are sometimes present in temporal lobe tumors as a result of irritation of the olfactory cortex in the uncinate gyrus. This usually occurs as a paroxysmal discharge which is part of a focal epileptic attack and is often associated with other phenomena especially auditory or visual. The hallucination is most frequently a disagreeable one.

The second cranial nerve or the optic nerve is the special sensory nerve from the retina. Testing of its function forms one of the most important parts of a neurological examination and may show signs of extreme value from the standpoint of both anatomical and pathological diagnosis. In the first place the fibers of this nerve can be seen on ophthalmoscopic examination and when intracranial pressure becomes increased the nerve head or optic disc becomes visibly swollen and edematous. Normally this optic disc (Fig. 386) is a sharply outlined yellowish white circular area but when swollen it

the anterior corpora quadrigemina, but these are concerned with reflexes and not with visual perception. Because of its long and partially crossing course interruption of the visual pathway at various locations will produce characteristic defects in the fields of vision.

These defects are represented in Figs. 387 in which hypothetical lesions have been placed at different points and the field defects corresponding to each lesion have been charted. A lesion of the optic nerve (A) causes blindness in the homolateral eye. A lesion in the chiasm (B) if complete, as occurs characteristically in tumors of the pituitary gland causes a bitemporal hemianopsia while if the involvement of the chiasm is not complete (C) the defect will vary in distribution. Lesions in the optic tract (from the optic chiasm to

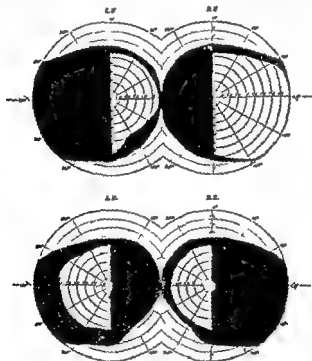


FIG. 388.—Above: Left homonymous hemianopsia with sparing of central vision. Below: Right homonymous hemianopsia with sparing of central or macular vision. (From Field, Evans and MacVillain, "Visual Field Defects in Man with Particular Reference to Macular Representation," *Neurology*, 1931, 1, 113.)

the external geniculate body) and in the optic radiation (from the external geniculate body to the calcarine cortex in the occipital lobe) will produce a contralateral homonymous hemianopsia as indicated. Quadrantic defects follow lesions (E and F) involving only part of and not the entire, optic radiation.

With lesions of the optic nerve or optic tract resulting in complete blindness of the entire field (A) or part of the field (B, C and D) the pupillary light reflex (described later) cannot be obtained from the blind part of the retina. To determine the absence of this requires special apparatus which will project a light on a restricted portion of the retina and this test is rarely performed. With these lesions also macular or central vision is split or hemianopic like the remainder of the field.

Acuity of vision is usually diminished when papilledema or swelling of the optic disc is present, but the impairment may be greatly out of proportion to the swelling and may consist only of an enlargement of the physiological blind spot. With progressive optic atrophy, either primary or secondary, diminished acuity goes on to blindness. In the amauroses and amblyopias of toxic or other origin acuity is also diminished.

Examination of the fields of vision is particularly valuable from a localizing standpoint. The retinal fibers which form the optic nerve undergo a partial crossing in the optic chiasm. Fibers from the nasal half of each retina

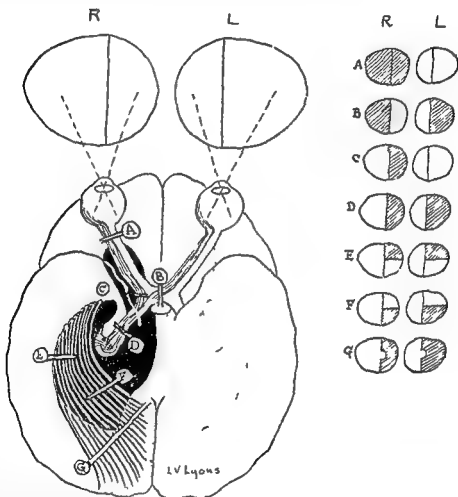


Fig. 38.—Diagram of the visual pathway and the visual field defects from lesions in various parts of the visual pathway. (Adapted from Horsman.) A Lesion of right optic nerve—blind spot in right eye. B Lesion of the optic chiasm—blind spot in both eyes. C Lesion of the outer part of the optic tract—blind spot in right eye. D Lesion of the right optic tract—blind spot in right eye. E Lesion of the right optic tract—blind spot in right eye. F Lesion of the right optic tract—blind spot in right eye. G Large lesion of right optic tract—blind spot in right eye. (From Brock. The Basis of Clinical Neurology. Williams & Wilkins, Baltimore, 1939.)

cross while those from the temporal halves do not (Fig. 387). The optic tract so formed on each side terminates in the external geniculate body. New neurones there take up the function and carry the visual perceptions to the striate or calcarine cortex in the occipital lobe. Apart from the fibers of the optic tract which terminate in the external geniculate body, others go to

of the occipital lobes are fused into a perception of a single object. Further more the object is perceived in three dimensions length, breadth and thickness. our vision is stereoscopic. If however due to the paralysis of an external ocular muscle a strabismus or squint is present then the two images will remain separate in consciousness and the object will be seen double. The spatial relationship of the false and the true image will depend upon the muscle paralyzed and consequently the direction of the strabismus. Furthermore the distance between the false and the true image will increase as the eyes move in the direction of the pull normally exerted by the paralyzed muscle. This is easy to prove by looking at an object and then passively pushing one eyeball out of position when the object will be seen double. The reason for this is that the two images of the object do not fall on similar or corresponding points of the retinae to allow their fusion.

While paralysis of external ocular muscles is usually of localizing value sixth nerve paralysis alone either on one side or both, occurs frequently in increased intracranial pressure without indicating the location of the lesion. The intracranial course of the sixth nerve is long and its liability to paralysis when general pressure within the skull is increased is due either to a pull upon the nerve or to compression of it by the posterior cerebral artery. When the paralysis is due to a focal lesion there are usually other signs with it such as involvement of the seventh or other cranial nerves or disturbances of conjugate eye movements (see below).

Apart from the paralyzes of individual movements of the eyes paralysis of conjugate movements may occur. The centers for conjugate movements are not fully known those for lateral conjugate movement are supposed to be in the vicinity of the sixth nerve nuclei and those for upward and downward movement in the midbrain perhaps in the anterior corpora quadrigemina. These are lower motor neurone centers and when they are destroyed conjugate movement (or movement together) of the eyes both voluntarily and reflexly is abolished. Upper motor neurone centers exist but are mostly unknown. The frontal abductive field (see p 1007) is an upper motor neurone center for lateral movements and stimulation of it causes forced conjugate deviation toward the opposite side. Paralysis of this center causes forced deviation toward the side of the lesion because of the unopposed action of the opposite center. In the same way stimulation of the cortex in the region of the angular gyrus will cause conjugate eye movements to the opposite side. In paralysis of voluntary conjugate movement following an upper motor neurone lesion, reflex conjugate movement is still possible and if the eyes are fixed upon an object and the head then turned passively the eyes will remain fixed upon the object even though this necessitates conjugate deviation in a direction in which it cannot be carried out voluntarily. In addition though conjugate movement in a certain direction is impossible individual movement of each eye in the same direction can be carried out. The posterior longitudinal bundles which extend from the midbrain down into the cervical cord and which connect up the nuclei of the third fourth and sixth nerves the vestibular nuclei and certain nuclei in the pons is the anatomical pathway

When the lesion causing the blindness is in the optic radiation, however, primary changes do not occur in the fundus and the light reflex is not lost as the lesion does not involve the reflex arc. If the lesion in the optic radiation is close to the external geniculate body, macular vision is split (Fig 388) but if it is more posterior, macular vision is preserved and the hemianopsia does not include macular or central vision. All these defects are predicated upon destruction of the entire pathway concerned but disease may pick out only part of the pathway and the result may be a quadrantia rather than a complete hemianopic defect.

An interesting point of differentiation between homonymous hemianopia following a lesion of the optic radiation and one following a lesion of the occipital cortex is that in the former the patient will be aware of a blank or blind area within his field, while in the latter there may be no such subjective defect except that objects in that area cannot be seen.

The macula is a point on the retina horizontally level with the disc and about two disc diameters to the temporal side of it. It is visible on ophthalmoscopic examination as a minute bright area which is avascular and surrounded by an area of duller red than the remainder of the retina. It is the point of greatest visual acuity and it is to bring light rays upon it that we look directly at objects and converge as we look at near objects. The preservation of the entire macular vision in lesions of the optic radiations has not yet been satisfactorily explained.

The third, fourth and sixth cranial nerves, or the oculomotor trochlear and abducens innervate the external ocular muscles and bring about eye movements. In addition the third nerve supplies the levator palpebrae superioris, which raises the upper eyelid, and also the constrictor muscle of the pupil. The third nerve supplies all the muscles for movement of the eye except the superior oblique which is supplied by the trochlear nerve, and the external rectus which is supplied by the abducens nerve. Impairment of extraocular movements causes strabismus and diplopia. The strabismus, or deviation of the eyeball from the normal position, is brought about through the unopposed action of the muscles which are intact and may not be observable with early or partial weakness. If the sixth nerve of one side is destroyed the external rectus muscle of the corresponding eye will be paralyzed the eye will be turned inward or toward the nose (internal strabismus) and outward or lateral movement of the eye will not be possible. If the entire third nerve is destroyed there will be a droop of the eyelid from paralysis of the levator palpebrae superioris a dilatation of the pupil from paralysis of the constrictor muscle of the pupil an external strabismus from the unopposed action of the intact sixth nerve and diplopia. Because the third nerve nucleus is a long one, which is subdivided into smaller nuclei concerned with the individual functions, involvement of it within the midbrain is usually incomplete and so only some of the muscles are paralyzed such as the levator palpebrae superioris or the constrictor muscle of the pupil. Isolated lesions of the fourth nerve are rare.

Because of the frontal position of our two eyes images of objects at which we look fall on both retinæ and yet the two images carried in to the cortex



cause of the distribution of fibers in the pons medulla and upper cervical cord, such impairment may result from lesions over a widespread area. Irritative lesions may also occur in one or more of the divisions and give rise to the condition known as *trigeminal neuralgia* or *tic douloureux*.

The motor nucleus of the fifth nerve also lies in the pons and the fibers supply the temporal masseter and pterygoid muscles. Paralysis of temporal and masseter muscles can be felt when the patient tightly clenches the teeth as the involved muscles will not contract. Paralysis of the pterygoid will cause the jaw to deviate toward the paralyzed side when the mouth is opened. The reason that the deviation of the jaw is to the paralyzed side is that opening of the mouth is an active movement not a passive droop and the unopposed action of the intact muscles forces the jaw over to the paralyzed side.

The seventh or facial nerve arises in the pons and after looping about the nucleus of the sixth nerve leaves the brain stem medial to the eighth nerve. It supplies all the facial muscles except those of mastication and the levator palpebrae superioris and also innervates the platysma and the stapedius muscles. In addition it affords passage to parasympathetic fibers through the great superficial petrosal nerve and carries sensory impulses through the nervous intermedius and taste from the anterior two thirds of the tongue by the chorda tympani.

There are two types of facial palsy: a peripheral or lower motor neurone paralysis or Bell's palsy, and a central or supranuclear or upper motor neurone paralysis. In the former all the facial muscles of expression are paralyzed on the side of the lesion. The forehead cannot be wrinkled, the palpebral fissure is wide and gaping and the lower eyelid falls loosely away from the eyeball so that tears which cannot reach the punctum lacrimale stream down over the cheek. The eye cannot be closed because of paralysis of the orbicularis oculi and in an effort to close it the eyeball rolls upward to expose a large area of sclera. The nasolabial fold is obliterated, the corner of the mouth droops and cannot be elevated. Whistling is impossible and because of paralysis of the buccinator muscle food collects between the teeth and cheek and is only with difficulty dislodged. If the lesion is sufficiently proximal to interrupt the fibers to the stapedius muscle and those of the chorda tympani there will be hyperacusis and a loss of taste sensibility over the anterior two thirds of the tongue. If such a peripheral lesion is complete the reaction of degeneration will be found in the muscles involved after an interval of twelve to sixteen days and faradic excitability will be lost. The presence of faradic response after such an interval is of good prognostic significance since it indicates that the lesion did not cause complete destruction of the nerve.

In the supranuclear type of facial palsy the disability is contralateral and is not as widespread nor as striking because bilateral innervation of the muscles allows some preservation of function. In this type of lesion the forehead muscles escape and the orbicularis oculi almost always does. If the orbicularis oculi is weakened it is only slightly so. The paralysis is practically confined to the corner of the mouth and even there the disability and

by which the action of these nuclei can be synchronized and made to work together in functional patterns

It has been stated above that the constrictor muscle of the pupil is supplied by the oculomotor nerve, this supply is by parasympathetic fibers. Dilation of the pupil is brought about by sympathetic fibers from the cervical sympathetic chain. The pupils constrict when exposed to light (light reflex) and dilate in darkness and they also constrict on looking at a near object (accommodation reflex). In addition to the constriction of the pupil on looking at a near object the eyes converge so as to project the image on to the macula of each eye. In certain diseases of the central nervous system, notably syphilis, the reaction to light is abolished, and that to accommodation retained. This is the chief feature of the Argyll Robertson pupil which is further discussed under the heading of Syphilis of the Nervous System. Why this dissociation of reflexes occurs is not exactly known, but it may be due to a predilection for the disease to involve only those fibers of the optic nerve concerned in the light reflex, or to the involvement of midbrain centers, such as the Edinger Westphal nucleus concerned only with the reflex to light and not with that to accommodation. A condition which may be confused with Argyll Robertson pupils is that of tonic pupils (Adie's syndrome), in which the reaction to light is extremely slow, so slow in fact that it may be thought to be absent. It is frequently associated with absence of tendon reflexes which makes its resemblance to tabes dorsalis more confusing. The significance of this is not known but it seems to be unimportant from the standpoint of health.

The fifth cranial nerve, or the trigeminal, is sensory to the face and motor to the muscles of mastication. The sensory fibers are collected into three branches, the superior or first or ophthalmic, the middle or second or maxillary and the inferior or third or mandibular. These three branches unite in the Gasserian ganglion which lies on the floor of the middle fossa of the skull. The sensory root from this ganglion enters the pons and divides into two parts, one of which enters the sensory nucleus in the pons and the other descends to the cervical spinal cord. From both the pontine nucleus and the nucleus of the descending tract of the fifth nerve fibers cross to the opposite side ascend and enter the ventral nucleus of the thalamus. The first division carries sensation from the anterior part of the scalp the forehead eyelids, lacrimal glands and the conjunctiva. The second division supplies the cheek upper lip and nose. The third division supplies the lower lip chin and the skin over the mandible except for a small area at the angle of the jaw which is innervated by the second cervical nerve. In addition the trigeminal nerve carries ordinary sensation from the mucous membrane of the mouth and nose and takes part in the formation of the nasociliary sphenopalatine otic and submaxillary ganglia of the autonomic nervous system. It is also the chief sensory nerve of the dura of the brain.

Sensation from the face may be impaired over the distribution of one or all of the branches of the fifth nerve in destructive lesions and when the first division is involved the corneal reflex will also be diminished or absent. Be

while in nerve deafness air conduction remains greater than bone conduction, but both are reduced. A vibrating tuning fork placed on the center of the forehead is normally heard equally on the two sides, as both auditory nerves pick up the vibrations transmitted to the skull (Weber test). In cases of obstructive deafness the sound of the fork is referred to the deaf ear and heard better there than on the intact side while in cases of nerve deafness the sound is referred to the good ear. Irritative lesions of the cochlear division of the eighth nerve occur frequently, both in labyrinthine disease and in disease of the nerve itself. In such cases tinnitus, or noises in the ears occurs. Sometimes both cochlear and vestibular branches are involved and with the tinnitus there will be vertigo.

Impulses arise in the vestibular portion of the eighth nerve following alterations in the rapidity and direction of flow of the endolymph in the semicircular canals induced by changes in the position of the head and irrigation of the external auditory canal with hot and cold solutions. These stimuli give rise to postural and righting reflexes concerned in the maintenance of equilibrium. The vestibular fibers enter the brain stem and terminate in several large nuclei which lie in apposition to one another. From these nuclei fibers go to the cerebellum, the posterior longitudinal bundles, the vestibulospinal tract and other nuclei in the reticular formation.

Irritation of the semicircular canals by rotation of the body or irrigation of the external auditory canal normally causes vertigo, nystagmus, a feeling of falling and sometimes nausea and vomiting. Fawcett has described 26 types of rotationally induced nystagmus depending upon the position of the head during rotation and so upon the combinations of semicircular canals stimulated on the two sides. A study of the responses to such turning and irrigation is often of great value in determining the integrity of vestibular connections and of influences which modify them.

Nystagmus consists of rhythmic movements of the eyes which are usually made up of a slow phase and a quick phase. The direction of the nystagmus is named after the quick phase although this is just a compensatory movement to overcome the slow movement which has taken place. Nystagmus occurs in some ocular diseases as partial blindness, paralysis of eye muscles, fatigue on fixation, etc. It occurs also in disease of the brain other than of the vestibular mechanism such as cerebellar and brain stem lesions and is then horizontal, vertical, skew or diagonal. Labyrinthine nystagmus is of a mixed horizontal rotary type of moderate amplitude and rapidity and of short duration. Irritative lesions of the labyrinth cause a nystagmus toward the side of the lesion and in destruction of the labyrinth the nystagmus is toward the intact side. For the occurrence of nystagmus only a very limited area of central nervous system is necessary, an area including the vestibular nuclei and the nuclei of the third and sixth cranial nerves. While this is so other areas of the central nervous system may modify it. Interpretation of the various types of nystagmus is a specialized subject beyond the scope of this book and such interpretation frequently aids in the localization of nervous disease.

the deformity are not so marked as in the peripheral cases. In lesions about the thalamus, the weakness may be present only on emotional movement and not on voluntary movement, while the reverse may be the case in lesions proximal to the thalamus.

When only partial recovery takes place in a case of peripheral facial palsy, or when recovery is long delayed, secondary contracture may take place in the paralyzed muscles. The palpebral fissure then narrows again and the involved corner of the mouth may be pulled up to a level higher than that of the intact side. Because of these contractures the patient may seem at first at least to be paralyzed on the intact side, as that corner of the mouth is lower, but when voluntary movements are attempted the imperfect movement on the involved side can be seen. Another complication of imperfect recovery is the inability to completely dissociate one set of movements from another. Thus such a patient on forcibly closing the eyes will elevate the corner of the mouth on the diseased side, or when voluntarily showing the teeth or elevating the corner of the mouth, or spontaneously laughing or smiling will partially close the corresponding eye.

Facial spasms and blepharospasms occur frequently as habit spasms or tics and sometimes also as a result of disease of the extrapyramidal system. The seventh nerve also carries deep pain and pressure sensibility from the face. Clinically this function is seldom deranged except in some cases of atypical facial neuralgia in which the continuance of pain after section of fifth nerve fibers is attributed to irritation of sensory fibers of the seventh nerve. While this may be so in some cases it is certainly not true in all.

The eighth cranial nerve or the auditory, is made up of two divisions a cochlear concerned with hearing and a vestibular concerned with the maintenance of equilibrium. The cochlear fibers enter the brain stem and, after making connections with nuclei there ascend on the two sides in the lateral lemnisci. These are distributed to the posterior corpora quadrigemina and the internal geniculate bodies, from the latter of which new fibers go to the transverse gyrus of Heschl on the dorsal surface of the temporal lobe. This gyrus is the cortical center for hearing and auditory sensations from each ear are distributed bilaterally.

Impairment of hearing or deafness may follow obstructive lesions in the channels carrying sound to the nerve endings in the internal ear or lesions in the auditory nerve itself. In the latter case when the deafness is slight it is for tones in the higher frequencies of sound vibrations and this can be determined by the use of a series of tuning forks or by means of the audiometer. Sound vibrations reach the auditory nerve both by air conduction and by bone conduction and normally the acuity of air conduction is greater than that of bone conduction. This is easily demonstrated by blocking the external auditory meatus with the finger and placing a vibrating tuning fork on the mastoid process, when the sound will be clearly heard. After the sound has disappeared, if the obstructing finger is removed and the fork placed opposite the open external auditory meatus it will again be heard (Rinne test). In obstructive deafness bone conduction becomes greater than air conduction,

rather than free and distinct association systems. In the introduction to this chapter the formation of gyri and convolutions and lobes separated by sulci and fissures was described.

The final answer to the question as to whether the cerebral cortex acts as a whole or whether strict localization of function resides in its various parts has not been given, but it has been established that strict localization is present in certain areas notably the pre-Rolandic motor cortex and the calcarine or striate cortex. On the other hand there are large areas of cortex the functions of which have not been determined and which are frequently referred to as 'silent' areas. By the study of the response to electrical stimulation, the pattern of focal discharges in epileptic attacks and the defects following ablation of cortical areas new knowledge is slowly being added to this subject.

The motor function of the pre-Rolandic cortex has been described already. Electrical stimulation of this area causes contraction of muscles on the opposite side of the body, and it is from the large Betz cells of this convolution that the pyramidal tract arises. It has occasionally been noted that electrical stimulation of the post-Rolandic convolution will also give rise to movements and much more rarely the same result has been noted on stimulation elsewhere. In the motor convolution the leg is represented uppermost, the arm and trunk in the middle and the face lowermost. Stimulation of the frontal adersive field in the posterior part of the first and second frontal convolutions causes turning of head and eyes to the opposite side and destruction of this area causes head and eye turning to the same side. Fulton and his coworkers have within the past few years published the results and conclusions from a large series of experimental lesions in the so-called premotor cortex or area 6 of Brodmann. They believe that ablation results in awkwardness or clumsiness especially of fine movements, forced grasping, vasomotor disturbances and increased tonus and tendon jerks on the opposite side of the body. The authenticity of this premotor syndrome has been questioned especially by Walshe who states that the only constant manifestation is forced grasping and that this requires an intact corpus callosum for its appearance.

It has long been tacitly accepted that the frontal lobes are the centers for highest psychic functioning and that ordinarily the left frontal lobe is especially dominant. It is surprising however how irregular and indefinite is the symptomatology following removal of a frontal lobe. Penfield and Evans who carefully studied patients after ablation of either the right or left frontal lobe not including the area electrical stimulation of which caused movements found very little disturbance. The patients showed no disturbance in micturition tone or reflexes and no forced grasping. Mental functions were very well preserved and the only impairment that could be found seemed to be in the 'processes prerequisite for planned initiative'. It is apparent therefore that the physiology of the frontal lobe is still a matter for careful research and it is the subject of much investigation at the present time.

The temporal lobe is one of the great sensory regions of the brain and in it are the cortical centers for taste, smell and hearing. The fibers subserving

The ninth and tenth cranial nerves, the glossopharyngeal and vagus, are closely associated and arise from common nuclei in the medulla. Motor fibers arise from the nucleus ambiguus and supply the constrictors of the pharynx the muscles of the soft palate and the vocal cords. Taste fibers from the posterior third of the tongue enter the nucleus solitarius, and other sensory fibers end in the dorsal vagus nucleus. Sensations from the upper respiratory tract and middle ear enter the brain stem through the ninth nerve. The vagus is a great parasympathetic nerve which is concerned with the function of the thoracic and abdominal viscera. In bulbar palsies, which are lower motor neurone lesions of the nerve supply from the medulla there are dysarthria, dysphagia and dysphonia. Glossopharyngeal neuralgia is manifested by paroxysmal pains like those of trigeminal neuralgia but situated in the throat. Eustachian tube and behind the ear, and individual attacks can be induced by certain movements of the soft palate and nasopharynx.

The eleventh cranial nerve or spinal accessory, arises in part from the medulla and in part from the cervical spinal cord. It innervates the trapezius and the sternocleidomastoid muscles. When these are paralyzed, the shoulder cannot be shrugged and the sternocleidomastoid muscle, which pulls the occiput downward and toward its own side, is also inactive.

The twelfth nerve or hypoglossal, is the motor nerve to the tongue and when it is paralyzed the protruded tongue deviates to the weak side. The reason for this is that protrusion of the tongue is an active movement and, if this is paralyzed on one side, the opposite overacts against no resistance and so pushes the tongue away. If the paralysis is a lower motor neurone one there will be atrophy of the tongue as well and this frequently occurs in bulbar paralysis. In such cases also fibrillary twitchings may be seen in the tongue. In supranuclear lesions atrophy does not occur. Occasionally in the normal individual the tongue tends to deviate very slightly to one side and in cases of peripheral facial palsy there may seem to be quite an appreciable deviation, but this is overcome when the mouth is pulled passively into a straight position while the tongue is protruded.

### The Cerebral Cortex

The cerebral cortex is made up of six layers of cells which vary in diameter from  $6\mu$  to  $120\mu$  or more. Depending upon the architecture of these six layers Brodmann was able to differentiate 52 distinct cortical areas and other observers notably Economo have described more. This great cellular mantle forms as far as is known the highest centers for cognitive function for emotional states and reactions and perhaps though it is not certain for consciousness itself. It is the final integrating center for all sensations that reach consciousness and the highest center for the initiation of reactions that are voluntarily performed. It sends fibers to lower centers (corticofugal fibers) and receives fibers from lower centers (corticipetal fibers) and by means of association fibers its various subdivisions are brought into communication with one another. The largest group of such association fibers forms the corpus callosum which joins the two hemispheres, though there is some evidence to support the belief that the callosal fibers are collaterals of other systems.

The study of focal epileptic discharges plays an important part in the investigation of cortical function and localization. Irritative lesions such as tumors, scars, vascular abnormalities and areas of atrophy characteristically set off paroxysmal discharges which manifest themselves outwardly as Jacksonian epileptic attacks.

Jacksonian epileptic attacks begin in one part, spread to contiguous parts and always follow the same pattern. The part in which they begin, or the function which they disturb first, will depend upon the focus from which they arise. An exact description of such an attack will usually allow a very accurate diagnosis of the site of the lesion. The irritative discharge having begun will spread as ripples spread when a stone is thrown into a smooth surface of water. At any time during their course these focal attacks may become generalized and they may or may not be associated with loss of consciousness which may be present from the beginning or supervene at any time during their progress.

Focal epileptic attacks arising from lesions in the frontal lobe are primarily motor. Usually the earliest phenomenon is a turning of the head and eyes away from the side of the lesion and then clonic convulsive movements beginning in one part and spreading to adjacent parts. If the discharging focus is high up in the frontal lobe, the convulsive movements will begin in the opposite foot, then spread to the arm and then to the face. If the lesion is in the vicinity of the arm motor center the movements will begin in the hand or arm and then spread to the face and the leg and the foot. In the same way, if the lesion is lower in the frontal lobe the attack will begin in the face, then spread to the arm and then to the leg. As noted above, the attack may at any time become bilateral and generalized and consciousness may or may not be lost at any time during the train of events.

Jacksonian attacks induced by a lesion behind the Rolandic fissure, in the parietal lobe manifest themselves first by sensory phenomena which may then be followed by convulsive movements. The reason is apparent as sensory cortex must be irritated before the discharge can pass over to the motor cortex. The sensations will be in a part as the movements do in motor attacks and spread to contiguous parts. They will be in the nature of a numbness or tingling. The focal manifestations will again be contralateral to the lesion.

The characteristic type of attack occurring in temporal lobe lesions is the uncinate fit. This consists of a bad taste in the mouth, the perception of a disagreeable odor and often visual phenomena. The odor and taste are not lateralized, but the visual phenomena are in the opposite visual field as one would expect. These visual phenomena vary from micropsia or macropsia (images become small or big) to highly systematized hallucinations. Sometimes the hallucinations are Lilliputian and the unreal objects that are seen are dwarfed and sometimes they are elaborate panoramas with a succession of figures appearing or events taking place. Frequently in attacks arising in the temporal lobe there are sucking or smacking movements of the lips. Sometimes also auditory phenomena such as noises occur and occasionally the attacks take the form of dreamy states.

these functions have complicated courses and are distributed to both temporal lobes so that a unilateral cortical lesion does not result in a loss of the function. Irritative lesions in the temporal lobe frequently produce a characteristic syndrome which is pathognomonic of the condition. Unilateral fits occur and these are described under the heading of focal epileptic manifestations and there is usually in addition a hemianopsia in the opposite visual field because of involvement of the optic radiations. When these radiations leave the external geniculate body they widen out into a large area part of which curves forward and laterally into the temporal lobe. If only part of this curving band is destroyed, the visual field defect will be a quadrant one instead of a full half field blindness.

The parietal lobe situated above the temporal lobe is also a large sensory area concerned with somatic sensibility. It has been stated that the sensory pathways terminate in the thalamus from which new thalamocortical pathways arise. Those concerned with somatic sensibility pass proximally through the posterior part of the internal capsule to reach the cerebral cortex. Most of the fibers are distributed to the post Rolandic convolution but others go to more posterior parts of the parietal lobe and also to the pre Rolandic cortex which as has been stated, is primarily motor. Dusser de Barenne was able to induce sensory changes in animals by local strychninization of both the pre Rolandic and post Rolandic areas. The same segmental arrangement has been described in the post Rolandic convolution as in the pre Rolandic motor area with leg uppermost arm and trunk in the middle and face and other cranial structures in the lowermost portion, but this is not as definite in its arrangement as in the motor cortex. Evans who carried out careful sensory studies on human beings after ablation of areas of cortex found that astereognosis and impairment of discriminatory sense necessary to appreciate differences in texture weight form and consistency occurred after ablations of areas in the region of the supramarginal gyrus. He proposed that primary cortical centers in the anterior parietal region are linked by association neurones with an integrative center at the highest cortical sensory level in the supramarginal gyrus and that in this integrative center transmutation of sensory impulses to psychic activity occurs. This view is somewhat similar to that of Campbell who considered that each perceptual sensory cortical center is surrounded or adjoined by a corresponding psychic sensory level.

In the occipital cortex the visual cortical center borders on the calcarine fissure and is easily distinguished by a thin macroscopic, white line of Bail larger, which runs through the grey matter and because of which the area is called area striata or striate cortex. In this region the visual fibers from the external geniculate body of the same side terminate and within it there is a strict localization of the fibers from the various quadrants of the retina. The final termination of the fibers from the macula has not yet been finally decided. The prevailing opinion is that they are distributed over a wider area and extend farther forward than the remainder of the visual fibers, but there is some evidence to suggest that they may have a bilateral representation in both occipital lobes.



Sensory aphasia consists of a difficulty or inability to understand spoken symbols as such. Hearing is not impaired and there is no difficulty in the perception of the word as a sound but it cannot be understood as a proposition. It is in this type of aphasia that speech is most grossly disturbed. The importance of sense perceptions as a guide to the proper functioning of motor activities is such that in this sensory disturbance motor speech functions are also almost always impaired. The sensory defect may be complete or it may be manifest only in complex situations which demand the understanding of propositional symbols.

Alexia and agraphia are defects in written speech comparable to sensory and motor aphasia in spoken speech. The former consists of a difficulty in understanding written words as symbols and the latter an inability to make use of written words for the expression of propositions. The defects vary from time to time as those of spoken speech. The writing of words and sentences spontaneously or to dictation or efforts to copy them from models shown may all be impaired. Letters are omitted from words or words from sentences or improper ones are used so that the result may bear little or no resemblance to what it should.

The same sort of difficulties may be apparent in the use of figures in arithmetical problems in the appreciation and use of musical symbols and in the appreciation and use of objects. Shown a match and a matchbox the patient may not be able to name either of them nor recognize the name when it is spoken to him or presented to him in writing but on the other hand he may be able to show perfectly by his actions that he knows the objects and how they are to be used and for what purposes.

While these subdivisions have been made it is important to realize that the complex function of speech is not something made up by the addition of certain circumscribed parts. It is a function based upon the integrity of certain sensory pathways carrying perceptions into cortical centers of centers of sensory elaboration which will build up these perceptions into conceptions brought into relationship with other conceptions of associational pathways interrelating the many nervous mechanisms involved of memory and general intelligence and of centers having to do with the translation of psychic processes into motor phenomena. The result is that there is not a speech center but a function of speech which depends upon the integration of many nervous mechanisms of different complexities.

It is reasonable then that when speech is impaired the impairment should manifest itself in all components of speech functions and this is almost always true. It is just as reasonable however that involvement of some of the subcortical connections and pathways concerned with the different functions involved may occasionally impair one modality of speech and leave the others almost intact and this does occur at times. Such a selective disorder occurs particularly with occipital lobe lesions which encroach upon or otherwise impair the functioning of the region of the angular gyrus. In such cases the speech defect is almost exclusively one of reading and writing and it is only after very careful examination that minimal defects in other speech functions can be found. In general it seems that lesions in the anterior part of the

In occipital lobe lesions the focal symptoms are visual and are perceived in the opposite visual field. They may take the form of lights or colored stars, etc. Following these paresthesiae, or instead of them, there is frequently a clouding or a blindness in a quadrant or hemianopic field.

### Aphasia

Disturbances of speech, or aphasia, constitute one of the most difficult problems in the realms of neurology and psychology. Speech, as distinct from articulation, is a function closely linked with other intellectual functions, but it may be impaired in nervous diseases without obvious defect in the remainder of intelligence. It is controlled by one cerebral hemisphere, the left hemisphere in right handed people, and the right hemisphere in left handed people, although there are numerous exceptions to the latter. No adequate explanation has been offered for this dominance of one hemisphere over the other. Since 1861, when Broca described a case of aphasia in a patient with a lesion in the posterior part of the third frontal convolution, an area since then associated with his name, the question as to whether specific cortical centers for speech exist has been a matter for controversy. Without entering into this controversy it may be stated that destructive lesions in the dominant hemisphere in an area extending from the posterior part of the third frontal convolution through the island of Reil the superior temporal convolution and into the angular gyrus, will produce aphasic manifestations.

These manifestations may be subdivided into the following groups: (1) disturbances in the initiation of spoken speech, motor aphasia, (2) disturbances in the reception of spoken speech, sensory aphasia, (3) disturbances in the initiation of written speech, agraphia, (4) disturbances in the reception of written speech, alexia. Such an arbitrary subdivision is not without danger because the occurrence of each of these groups as an entity is denied by many, and the very terms are anathema to them. On the other hand, it has the advantage of simplicity of description of these conditions as static phenomena.

Motor aphasia may be complete so that the patient cannot speak at all or it may be partial so that the patient although speechless is not wordless. The latter is the characteristic state and in it the use of words as propositions may be impossible although their use as expletives or in response to emotional stimulus remains. Sometimes the defect is so great that speech becomes an unintelligible jargon and at others it consists merely of a groping for the proper word, a difficulty in finding it and the use of improper terms in its place. Such patients speak slowly and are frequently aware of their inadequacy and their use of wrong words. Perseveration is often noted and the patient having used one term or answer in a certain situation will repeat it in following situations to which it is no longer applicable. A special type of motor aphasia is the so called nominal aphasia in which the defect is present only on attempting to name objects held up to view. It is characteristic of aphasic patients that their performance from day to day and from hour to hour varies greatly and for this reason frequent testing of their reactions in and to certain situations is important.

which arise from these ganglionic cells are the postganglionic fibers or the grey rami communicantes and are not myelinated. Some of the grey rami reenter the spinal nerves and carry vasomotor and secretory impulses to the skin and arteries of the extremities; others form nerves going to the plexuses in the thoracic and abdominal cavities. The afferent sympathetic fibers are not broken up in this way but pass from the organ directly into the spinal cord through the posterior nerve roots in the ganglia of which their cells are located; they are myelinated throughout.

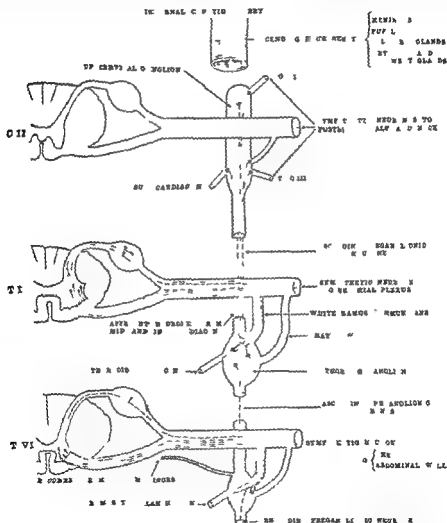


FIG. 389.—Diagram of the sympathetic nervous system. (From White, The Nervous System, The Macmillan Company, New York.)

The parasympathetic nerves made up of cranial and sacral divisions differ from the sympathetic in that they do not traverse the sympathetic ganglionated chain and that their postganglionic fibers arise from plexuses in the wall of the viscus that they are supplying. It has been shown that vasodilator fibers pass through the posterior spinal nerve roots but their exact nature has not yet been determined.

cortex concerned with speech will cause motor speech disturbances, in the posterior part, disturbances in reading and writing, and in the region of the temporal lobe and island of Reil marked disturbances in all types of speech

**Apraxia**, which is in many ways analogous to motor aphasia, is an inability to perform purposive movements on volition, depending, not upon a defect in the innervation for the several components of the act, but upon inability to combine these to carry out the act. Thus a patient with normal power, sensation and coordination may be unable to button his coat, although all the individual movements necessary can be done perfectly. In some cases he is no longer able to appreciate the purposive movement that should be carried out and, for example, if given a knife and fork will be entirely unaware of how they should be used. These defects seem to arise from impairment of function of cortical areas in the dominant frontal and parietal lobes.

### The Autonomic Nervous System

The autonomic nervous system should not be considered as something separate from the remainder of the nervous system. It has centers, afferent pathways, efferent pathways and intercalated pathways like the remainder of the nervous system. Its efferent axones pass out in the cranial nerves and the anterior roots of the spinal cord, and its afferent axones enter the brain and cord by way of the cranial nerves and the posterior nerve roots. It differs only in that it has different central nuclei and connections, a different mode of peripheral distribution and that it innervates different organs than the systems that have been considered above. It is divided into two main divisions which reach the periphery through the peripheral nerves in the following ways: the *craniosacral* or *parasympathetic* division sends fibers through the third, seventh, ninth, and tenth cranial nerves, and the second, third and fourth sacral roots; the *thoracolumbar* or *sympathetic* division leaves the spinal cord through the thoracic nerves and the first and second lumbar roots. In the diencephalon in the hypothalamic region, a group of nuclei exist which have been demonstrated to be the head centers for autonomic function. It is possible that pathways connect up these nuclei with cortical centers. This has not been proved but Fulton and his collaborators have described vascular and intestinal symptoms after ablation of the premotor cortex.

The sympathetic ganglionated chain lies close to the vertebral column on each side and extends throughout its length. At intervals along this chain sympathetic ganglia exist which correspond to the spinal nerves. In the neck the ganglia fuse into three: the superior cervical, the middle cervical which may or may not be present, and the inferior cervical which together with the first thoracic forms the stellate ganglion. In the thoracolumbar region from which the sympathetic fibers arise each anterior nerve root gives off a white *ramus communicans* which arose from the *intermedio lateral* group of cells in the corresponding segment of the cord and which is a preganglionic fiber (Fig. 389). These fibers enter the ganglionic chain where some synapse immediately with other groups of cells, some ascend or descend the chain to synapse in ganglia at different levels, and others pass through the ganglionated chain to synapse with cells in the splanchnic plexus. The nerve fibers

TABLE VIII

## THE SEGMENTAL MOTOR INNERVATION OF THE VISCERA

ORGAN	SEGMENTS WHICH GIVE OFF LARVAE			SEGMENTS WHICH GIVE OFF SYMPATHETIC NERVES													
	HIGHER			THORACIC												LUMBAR	
	CRANIAL SPINAL NERVE	THORACIC NERVE	4TH SACRAL NERVE	1	2	3	4	5	6	7	8	9	10	11	12	1	2
Eyes	+			+													
Salivary glands					+												
Blood vessels of meninges and brain							+										
Blood vessels of head and neck																	
Salivary glands of head							+				+						
Blood vessels sweat glands and erector pilae muscles of arms								+									
Heart							+										
Lungs		+					+										
Esophagus stomach liver pancreas and small intestine		+								+							
Adrenal														+			
Kidney															+		
Bladder																+	
Genitalia																	+
Sigmoid and rectum																	+
Blood vessels sweat glands and erector pilae muscles of legs																	+

F. O. White The Autonomic Nervous System The Macmillan Co

The autonomic nervous system innervates involuntary, smooth muscles and glands. This includes the muscles of the iris, the lacrimal glands, salivary glands, sweat glands and secretory glands of the gastrointestinal tract and of other mucous membranes, also the heart and blood vessels and the muscles and sphincters of the hollow viscera, the bronchi, gastrointestinal and genito-urinary tracts. It keeps the "milieu interieur" (Bernard) of the body constant and regulates the mechanisms concerned in heat production and loss, the mobilization of glycogen in the liver, the rate and force of the heartbeat, the peripheral arterial flow, the blood volume and hematopoiesis, the movement and evacuation of the abdominal viscera. These regulations, which together have been called "homeostasis" by Cannon, are mediated through the dual action of the sympathetic and parasympathetic divisions. The sympathetic system is the catabolic system that is called upon to meet emergencies and protect the body from them. It stimulates heat production, raises the level of the blood sugar, increases the rate of the heart, diminishes peripheral and so increases central blood flow, and inhibits the activity of the abdominal viscera. The parasympathetic is the anabolic or building up system the action of which is antagonistic to that of the sympathetic system. These functions may be influenced as a whole or in part.

Both the sympathetic and the parasympathetic systems can be influenced by drugs and by hormone secretions. The sympathetic system is stimulated by adrenalin and sympathin and depressed by ergotoxine, ergotamine and nicotine. The parasympathetic system is stimulated by pilocarpine, choline compounds and by pituitrin given intraventricularly and depressed by atropine and nicotine.

In recent years investigations by Dale, by Cannon and his coworkers, and by others, have shown that the action of the autonomic nervous system is brought about by means of chemical mediators which are set free when the system is stimulated. Thus stimulation of the sympathetic system causes the liberation of sympathin, which, by cross circulation experiments and by its action on denervated organs, has been shown to stimulate those structures ordinarily stimulated by the sympathetic nervous system and to inhibit those ordinarily inhibited. Its site of action is somewhere between the nerve ending and the organ itself as it is effective even after the nerve endings have degenerated. It is readily diffusible in the blood and so can cause a wide spread response after a limited stimulation. In the same way a substance is released when the parasympathetic system is stimulated. This is a choline compound which is very quickly destroyed and the activity of which is consequently restricted.

The following two tables from White\* are included to show the segmental innervation both motor and sensory of the autonomic system.

Because of its widespread distribution and of its importance to the proper functioning of the internal organs the autonomic nervous system forms an integral part of every other system in the body. Recent studies have indicated a close relationship between impairment of sympathetic function and many diseases, and efforts to correct this by surgical means have often been

involved. Disease in the nervous system may produce multiple or diffuse involvement as in disseminated sclerosis or single focal lesions as in new growths. In the latter case the correct anatomical diagnosis depends upon finding the location in which one lesion will involve several cell groups or tracts at the same time so as to produce the physical signs that are manifest. In the same way vascular lesions when single must be located in a region that will explain their symptomatology upon a single destructive focus. Apart from the general multiple or diffuse diseases and the single focal ones, there are certain diseases which characteristically pick out certain functional units and involve them alone such for example as progressive muscular atrophy which involves the motor cells in the anterior horns of the spinal cord or subacute combined degeneration which involves the pyramidal tracts and posterior columns of the cord.

In the sections dealing with disturbances of motility this aspect of the anatomical diagnosis became apparent in the explanation of crossed paralyses. These paralyses involving a cranial nerve on one side and the arm and leg on the opposite side could be due to a single lesion in only one location the level of origin of the cranial nerve involved on the same side. If it were higher than this the cranial nerve involvement must be contralateral the same as the paralysis of the arm and leg whereas if it were lower the cranial nerve would escape altogether.

In the same way in cases of thrombosis of the posterior inferior cerebellar artery because of involvement of the area in the medulla supplied by this artery a group of physical signs occur which must be in relation to a lesion there and not elsewhere. These signs vary somewhat depending upon the exact distribution of the artery but the characteristic syndrome consists of (1) hemianalgesia and thermal hemianesthesia alternans the distribution being most often over the face on the side of the lesion and over the body contralaterally this results from involvement of the descending nucleus and tract of the trigeminal nerve and of the spinothalamic tract (2) homolateral laryngo-velo-palatine palsy from involvement of the nucleus ambiguus (3) Horner's syndrome (constricted pupil narrow palpebral fissure and enophthalmos) from paralysis of fibers to the cervical sympathetic chain on the side of the lesion (4) usually some cerebellar signs on the side of the lesion from involvement of the inferior cerebellar peduncle (Russel and Stavrakys).

Lesions in the cerebellopontine angle especially eighth nerve tumors characteristically cause tinnitus and later nerve deafness from direct involvement of the auditory nerve cerebellar signs on the same side of the body from direct involvement or pressure on the cerebellum and its pathways and pyramidal tract signs on the opposite side of the body from pressure on the pyramidal tract before its crossing in the medulla. Of course all these signs may or may not be present depending upon whether the fiber tracts named are involved or not and in addition adjacent cranial nerves may be included in the lesion.

Single focal lesions in the cord can in the same way and usually do involve several structures. Compression of the cord by an extramedullary tumor usually produces as its first symptom girdle pains or root pains from

followed by excellent results. This branch of surgery has been exploited particularly in the treatment of peripheral vascular disease and also in retinitis pigmentosa, myopia, ptosis, hypertension, Mieschsprung's disease, peptic ulcer and in intractable pain arising from the viscera.

TABLE XIV  
SENSORY INNERVATION OF THE VISCERA

ORGAN	SUPERFICIAL AREAS TO WHICH PAIN IS REFERRED	SEGMENTS AT WHICH VISCERAL AFFERENT NEURONES ENTER SPINAL CORD	AUTHORITY
Meninges	Side of scalp and face	T <sub>1</sub> T <sub>2</sub>	Dandy (1931)
Heart	PreCORDIUM and inner arm	T <sub>1</sub> T <sub>2</sub>	Mackenzie (1923), White, Garrey and Athlone (1933)
Lung	No evidence of pain till parietal pleura and intercostal nerve are involved	---	White (unpublished data)
Esophagus	Substernal distress	T <sub>1</sub> T <sub>2</sub>	von Gaze (1924)
Liver and Gallbladder	Right upper quadrant distress with pain referred to right scapular region	T <sub>1</sub> T <sub>2</sub>	von Gaze (1924)
Stomach	Epigastric region	T <sub>1</sub> T <sub>2</sub>	von Gaze (1924)
Small Intestine	Umbilical region	T <sub>2</sub> T <sub>3</sub>	von Gaze (1924)
Colon	Suprapubic region	T <sub>4</sub> L <sub>1</sub>	Lawen (1923) von Gaze (1924)
Kidney	LoIn and groin	T <sub>4</sub> L <sub>1</sub>	von Gaze (1924) White and Garrey (unpublished data)
Ureter	LoIn and groin	L <sub>1</sub> L <sub>2</sub>	Lawen (1923) Whurton (1932)
Bladder	Suprapubic region	T <sub>4</sub> L <sub>2</sub>	Pieri (1926) Learmonth (1931)
Uterus	Suprapubic region and lower back	T <sub>4</sub> L <sub>2</sub>	Cleland (1933)

While it has been demonstrated that the sympathetic rami from the bladder and ureter reach the ganglionated chains as low as their fourth lumbar segments this does not imply that sensory impulses run into the cord as low as this. Indeed Head and Riddock's (1922) observations on the areas of referred pain from the bladder point to the first or second lumbar segments as the lower limit. (From White, The Autonomic Nervous System, The Macmillan Co.)

### Summary

The foregoing sections have been devoted to an explanation of the symptomatology following diseases of the chief nuclei and fiber pathways of the nervous system. By the proper interpretation of the symptomatology one is able to determine in large measure the structures that are involved and where in their course they are involved and consequently to locate anatomically the disease process. This is the clinical application of the known facts in regard to neuroanatomy and neurophysiology. From the standpoint of description and explanation it has been necessary to deal with the individual systems separately, but disease ordinarily does not restrict its ravages to one system and allow the others to remain free. The problem of anatomical diagnosis becomes therefore a plural one. It is more often than not a question of which several pathways are involved and where in their courses they are



the preservation of afferent impulses from the muscles so that it is a true reflex. In addition certain postural arrangements can be produced by impulses arising from muscles in the neck and from impulses arising in the labyrinth. These impulses are induced by altering the position of the head relative to the body after the semicircular canals have been destroyed (tonic neck reflexes) or by turning of the head in space without altering its relative position to the body, or after the sensory nerves from the neck have been destroyed (tonic labyrinthine reflexes). Apart from the extensor rigidity and the reflexes described above, the ability to reflexly right the body when its position has been altered is also lost. The righting reflexes are lost because of separation of midbrain nuclei from the lower centers and the reflex postures are induced through the mediation of brain stem nuclei separated from the inhibiting and modifying influence normally exerted by higher centers.

### THE PATHOLOGICAL DIAGNOSIS OF NERVOUS DISEASES

Because of the distinctive cells, the nerve cells and interstitial cells which occur in the nervous system pathological conditions produce changes which are different and more complex than those elsewhere in the body.

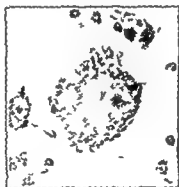


Fig. 240.—Central chromophobe cell (retrograde) (nerve cell) (nucleus cell from the nucleus ambiguus in case of amyotrophic lateral sclerosis) (cell of the nucleus ambiguus with rich at periphery of swollen cell) (nucleus situated dorsally and medially swollen) (From Weil's Textbook of Nervous Pathology, 2nd and 3rd editions, Philadelphia, 1922).

It has been stated that the nerve cells vary in size and shape and that they have an efferent process called the axone which is usually covered with myelin. In addition other processes called dendrites are present but these are expansions of the cell body itself and have the same structure. Fixed and stained nerve cells have a nucleus and nucleolus, chromophilic granules called Nissl granules and neurofibrils. The Nissl granules are present in the cell body and dendrites but not in the axone or the region about its origin from the cell body. Neurofibrils are seen to traverse the cell body and all its processes. When an axone, covered with myelin, leaves the central nervous system to pass into the peripheral nerves it acquires another covering the neurilemma or sheath of Schwann which has nuclei along its course. At regular intervals along this sheathed nerve there are constrictions called nodes of Ranvier and each area of the sheath of Schwann between these nodes is nucleated.

**irritation of the posterior nerve roots** These pains are present, either on one side or both, in the segmental distribution of the nerve roots involved. The paths within the cord which appear to be most vulnerable to the effects of such compression are the pyramidal tracts, and signs of their involvement may be present as the only evidence of the lesion for some time. A hemisection of the cord, or a lesion involving one half of the cord, will cause a Brown Sequard paralysis. In the segmental distribution of the lesion and on the same side there will be (1) a loss of all forms of sensation, from involvement of the posterior nerve roots (2) a lower motor neurone type of paralysis from involvement of the anterior horn cells and their axones passing into the anterior roots. The level symptoms from involvement of the tracts in the white matter, and these are the characteristic manifestations of this syndrome, will be (1) a homolateral, spastic, upper motor neurone type of paralysis below the lesion from involvement of the pyramidal tract, (2) a loss of position and vibration sensibility on the same side of the body at all levels below the lesion from involvement of the posterior columns and (3) a loss of pain and temperature sensibility on the opposite side of the body at all levels below the lesion, from involvement of the spinothalamic tract.

Complete sudden transection of the spinal cord results in a temporary condition of "spinal shock" in which all reflexes are absent, tonicity is lost and sphincter control is abolished. As all the fiber pathways have been sectioned there is of course an abolition of all voluntary motor power and of all sensation below the lesion. After an interval which may be long in man this condition of shock begins to wear off and certain reflex activities mediated by centers below the transection, begin to return. Tonus begins to return to the limbs and stimulation of the legs or feet or frequently at any point below the transection, will cause a triple flexion mass reflex of the legs. This is a defense reaction and may occur on both sides after unilateral stimulation. Its chief feature is withdrawal of the limb by means of flexion at the hip, knee and ankle. When the plantar response first returns it is a flexor response which gradually is replaced by plantar extension. The mass flexion reflex may be induced by the lightest of stimulation even the weight of a sheet, and may be so forcible and marked as to be accompanied by evacuation of the bowels and bladder and by profuse perspiration below the level of the lesion. Spastic paraplegia (upper motor neurone paralysis of both legs) due to an incomplete lesion of the cord may leave the legs in a position of extension or of flexion. The former is the more common and the latter position is attributed to a constant stream of stimuli entering the cord and causing a constant triple flexion reflex of the legs which remain in a position of flexion. This paraplegia in flexion is believed to be due to involvement of the vestibulospinal pathways in addition to the pyramidal tracts while paraplegia in extension is supposed to occur when the vestibulospinal tracts escape.

Section of the brain stem at a point distal to the red nuclei and proximal to the vestibular nuclei produces a condition of decerebrate rigidity. This is manifested by a marked increase in tonus of extensor muscles the muscles which maintain an erect or standing position and act against gravity. Because of this, reflex standing occurs and the maintenance of this depends upon

the preservation of afferent impulses from the muscles, so that it is a true reflex. In addition certain postural arrangements can be produced by impulses arising from muscles in the neck and from impulses arising in the labyrinth. These impulses are induced by altering the position of the head relative to the body after the semicircular canals have been destroyed (tonic neck reflexes) or by turning of the head in space without altering its relative position to the body, or after the sensory nerves from the neck have been destroyed (tonic labyrinthine reflexes). Apart from the extensor rigidity and the reflexes described above the ability to reflexly right the body when its position has been altered is also lost. The righting reflexes are lost because of separation of midbrain nuclei from the lower centers and the reflex postures are induced through the mediation of brain stem nuclei separated from the inhibiting and modifying influence normally exerted by higher centers.

### THE PATHOLOGICAL DIAGNOSIS OF NERVOUS DISEASES

Because of the distinctive cells the nerve cells and interstitial cells which occur in the nervous system, pathological conditions produce changes which are different and more complex than those elsewhere in the body.



Fig 360—Central chondrocyte (large rounded cell) and ganglion cell from the nucleus ambiguus (smaller, more irregular cells). Crevellolet. Nuclei are well preserved at periphery of swollen cells like in center. Nucleus tufted centrally and mildly swollen (F. M. W. L. Textbook of Neuropathology, 2nd ed. F. B. Croft Philadelphia 1933)

It has been stated that the nerve cells vary in size and shape and that they have an efferent process called the axone which is usually covered with myelin. In addition other processes called dendrites are present but these are expansions of the cell body itself and have the same structure. Fixed and stained nerve cells have a nucleus and nucleolus, chromophilic granules called Nissl granules and neurofibrils. The Nissl granules are present in the cell body and dendrites but not in the axone or the region about its origin from the cell body. Neurofibrils are seen to traverse the cell body and all its processes. When an axone covered with myelin leaves the central nervous system to pass into the peripheral nerves it acquires another covering the neurilemma or sheath of Schwann which has nuclei along its course. At regular intervals along this sheathed nerve there are constrictions called nodes of Ranvier and each area of the sheath of Schwann between these nodes is nucleated.

Pathological processes will produce changes in all these structures. Interruption of the axone or disease affecting the cell body will produce alterations in the cell. Ordinarily this consists of swelling of the cell body which becomes spherical. The nucleus, which is normally located in the center of the cell, becomes displaced to one side. The Nissl granules undergo chromolysis and gradually disappear either from the center of the cell or its periphery (Fig 390). If the damage is not too great the changes reverse and the cell returns to normal. As cell disintegration continues, it is hastened by phago-

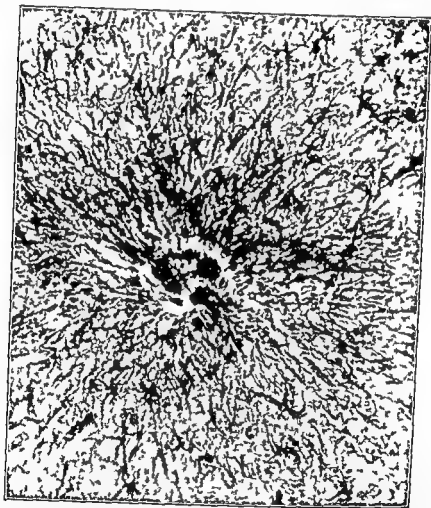


Fig. 391.—Glab wound of left hand lacerating in brain of rabbit, showing concentric arrangement of astrocytic expansion toward the connective tissue core. Cajal's gold chloride stain. (From "Principles of the Pathology of Neurosurgery" by L. C. Leafe, M.D., and J. H. Thompson, M.D., 1913.)

cytic cells which also remove the debris, and this process is called neuronophagia. The end result is either atrophy, which leaves only a shadow cell behind, or complete disappearance of the cell. Separation of the axone from its cell, either by damage of the former or disease of the latter, will result in Wallerian degeneration in the part of the axone separated and also a retrograde degeneration from the point of separation up to the next node of Ranvier. The myelin sheath undergoes changes and the myelin becomes broken up into droplets which are removed by phagocytic cells. The axone

also disintegrates and is removed. In the central nervous system where the axones have no sheath of Schwann this process is an irreversible one and regeneration cannot occur. In the peripheral nerves on the other hand, the degenerative changes in myelin and axone are coincident with regenerative efforts in the sheath of Schwann, the nuclei of which increase. As long as continuity remains in this sheath, or if it be reestablished regeneration is possible. Consequently peripheral nerves can regenerate while central pathways cannot. This type of Wallerian degeneration has been of great value in the study of neuroanatomy. Experimental lesions will cause the degeneration and while this is progressing distribution of the nerve fibers and tracts can be followed by special staining methods, especially the Marchi method.

Astrocytes are fibrous or nonfibrous (protoplasmic). The former are present chiefly in white matter the latter in grey matter. They are large stellate cells which have numerous processes a large pale nucleus and no nucleolus. Characteristic of them is the fact that they have one or more perivascular or pial feet attached to blood vessels or pia. Acute degenerative changes in the astrocytes consist of swelling of the cell body and its expansions, the latter of which gradually break off piece by piece to leave behind an ameboid cell body. The most acute change according to Cone is a fragmentation of the expansions of the cell with little or no swelling. In areas of softening or inflammation or degeneration the astrocytes multiply and form a wall around the lesion. Later the cells shrink and leave a dense network of glia fibers containing few cell bodies (Fig. 91). The astrocytes take no part in phagocytosis.

Oligodendroglia, so called because they have few expansions have little cytoplasm and no perivascular or pial feet. They occur in long parallel rows between myelinated fibers and as perineuronal satellites. As suggested in the introduction to this chapter they may be concerned with the formation and preservation of myelin. Penfield and Cone were the first to fully describe acute swelling of oligodendroglia a pathological change which is found in acute intoxications certain mental diseases (Elvidge and Reed) and in patients who have died in coma. This change is apparently a reversible one in which the cell becomes swollen pale and vacuolated (Fig. 92). The processes break up into granules and even the cell membrane may disintegrate and leave a naked nucleus behind. Apparently this change is a very sensitive one as it may be present without any changes in other cells. On the other hand acute changes in astrocytes are practically always accompanied by alterations in oligodendroglia.

Microglia cells are of mesodermal origin and develop chiefly immediately after birth. They are small cells with expansions containing spines at right angles and have an elongated triangular or curved nucleus. They have no fibrils and no foot plate. They are more numerous in the grey than in the white matter and are sometimes closely applied to nerve cells as satellites though this is more characteristic of oligodendroglia than of microglia. Microglia cells become ameboid and phagocytic in disease and carry products of disintegration of myelin and of broken up astrocytic expansions to blood vessels. It is presumed that they discharge these waste materials into the

blood vessels on the walls of which the fully laden cells congregate. These phagocytic cells are called compound granular corpuscles or scavenger cells, and are formed through swelling of the microglia which become rounded and withdraw their processes (115, 193). They also form elongated rod cells such as are found in the brains of paretics.

Just as the anatomical diagnosis of nervous diseases depends primarily on a proper interpretation of the physical signs, so the clinical pathological diagnosis is made largely from the history of the illness and the results of special examinations. These diseases etiologically may be subdivided into the following groups:



FIG. 1. --Extreme swelling of three oligodendroglia cells which are perineuronal at life. Small granules and vacuoles representing broken up expansions are present. Silver carbonate stain for oligodendroglia. (From Cone, "Acute Pathological Changes in Neuroglia and in Microglia," Arch. Neurol. and Psychiat. July 1928.)

1 Diseases due to prenatal influences or to familial constitutional defects. In these the history frequently though by no means always dates from the time of birth. This is particularly true in the prenatal diseases which are not familial as spina bifida with meningeal protrusions. In the familial diseases symptoms may be noticed from early infancy as in amaurotic family idiocy from childhood or youth as in Friedrich's ataxia or not until mature adult life, as in Huntington's chorea. Some of these prenatal conditions are developmental defects such as incomplete or imperfect development of certain parts of the nervous system some are diseases transmitted to the offspring

such as congenital syphilis, while still others are truly hereditary and transmitted in the germ plasma

2 Traumatic diseases may be acquired at the time of birth or any other time during life. The history of symptoms immediately following a trauma in an individual previously healthy is of course of great value in pointing to their cause. It must be borne in mind, however that trauma may be sustained at the onset of a nontraumatic illness such as during an epileptic attack or at the onset of a sudden vascular lesion in the brain. In these cases subsequent symptoms may be due to the trauma or to the coexistent disease. The use of x rays and of lumbar puncture are of great aid in determining the traumatic nature of neurological signs. Apart from the symptoms which supervene at the time of the accident there may be immediately or as long delayed as several years posttraumatic sequelae such as epilepsy, whose relationship to the trauma may be hard to determine.

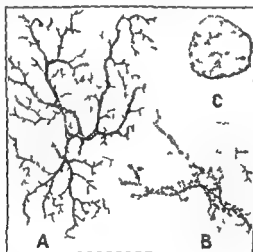


Fig. 1.—Trauma at age 9 from the meningitis. A. The cortical area of the brain. B. The brain. C. The brain. (From the Principles of the Pathology of the Brain, by Thomas Nelson and Son, New York, 1913.)

3 Acute inflammatory diseases may or may not be due to a demonstrable infection or infestation with parasites. In these cases the history is usually a short one and it is frequently possible to point to infection elsewhere in the body such as tuberculosis or acute middle ear suppuration which may have spread to the nervous system. Lumbar puncture is of great value in the diagnosis of these conditions when they are in communication with the subarachnoid space in which the cerebrospinal fluid circulates. Usually on physical examination other evidence of the inflammatory process is apparent such as fever. The chronic inflammatory diseases notably syphilis also cause changes in the cerebrospinal fluid.

4 Intoxications may occur from endogenous poisons as in delirium or from exogenous poisons. In the latter cases signs may follow within a short time of the assimilation of the poison as in alcoholism or after a very long interval as in lead poisoning. It is often possible in these cases to obtain

■ history of exposure to the poison or to find signs elsewhere in the body, in the blood, or in the excreta, which point to the cause of the disease

5 New growths are usually single focal lesions. They may be metastatic from elsewhere in the body or, more frequently, primary in the nervous system. The history in these cases is usually a long one extending over a period of months but sometimes symptoms may come on suddenly even though the tumor has been growing silently for a long time. The history of progression over a period of months, the signs of a single focal lesion, the evidence of increased intracranial pressure and findings on x ray examination all help to establish the diagnosis. If the tumor is in the spinal cord, or compressing the spinal cord, the Queckenstedt test and the use of lipiodol, both of which are discussed later, may be of aid. The characteristic symptoms which occur with increased intracranial pressure are headache, vomiting and papilledema or choked optic discs and are described on page 1101. The cause of increased intracranial pressure is usually a growing neoplasm which adds to the intracranial contents. Other causes also exist such as hydrocephalus, which may be due to any lesion which blocks the exit of cerebrospinal fluid from the ventricles or interferes with its absorption in the dural sinuses.

6 There is a large group of chronic degenerative diseases which affect the nervous system and the etiology of which is unknown. Usually these are slowly progressive over a period of years and usually also they are multiple or diffuse. Because of their predilection to involve only certain structures as in amyotrophic lateral sclerosis, or the history of their course, as in disseminated sclerosis, they ordinarily fall into groups of definite disease entities. For this reason and also because of their long continued course, their diagnosis is not usually difficult.

The pathological changes which occur in the various nervous diseases are described under the heading of the specific disease.

### The Cerebrospinal Fluid

The cerebrospinal fluid is formed by vascular tufts, the choroid plexus, which project into the ventricles and circulates throughout the ventricular system and in the subarachnoid space of the brain and cord. It escapes from the ventricles through the foramen of Magendie and the foramina of Lushka situated in the roof of the fourth ventricle. The subarachnoid space is not equally deep throughout, as it widens out at the base of the brain around the medulla oblongata, and in other locations, into large cisterns. The fluid is absorbed almost entirely through the arachnoidal villi which are projections of arachnoid into the venous sinuses in the folds of the dura. In addition it is probable that some of it is absorbed by lymphatics, which it reaches through the funnel like prolongations of arachnoid at the beginning of the cranial and spinal nerves.

The formation of this fluid is partly in the nature of a selective filtration and partly a secretion. It differs in composition from blood plasma but contains no new substance that is not in the blood. Because of the water cushion which it forms about the central nervous system it protects the brain and cord from ordinary jars and concussions. In addition it allows the brain



to vary in volume even though it is enclosed within a rigid bony box. Increase in volume of the brain forces cerebrospinal fluid into the spinal subarachnoid space and diminution in volume of the brain allows more fluid to collect in the ventricles and cranial subarachnoid space. This mechanical function of the cerebrospinal fluid is not its only one as it is also concerned in the metabolic processes going on in the nervous system. The volume of fluid is about 120 cc., and this may be replaced four or five times in twenty-four hours.

Cerebrospinal fluid may be collected for examination from the subarachnoid space below the termination of the spinal cord (lumbar puncture) from the cisterna magna at the base of the brain (cisternal puncture) or from the ventricles (ventricular puncture). Lumbar puncture is carried out by inserting a needle in the midline of the back through an interspace between two of the lower lumbar vertebrae and into the subarachnoid space within the vertebral canal. Ordinarily the interspace chosen is the third which is on a level with a line joining the uppermost portion of the two iliac crests. The puncture can be done with the patient seated or lying on his side. If pressure determinations are of importance in the specific case and they usually are the patient should be recumbent. Cisternal puncture is made with the patient lying on his side with his head flexed by inserting a needle in the midline of the back of the neck between the lowest point of the occiput and the spine of the atlas. As the needle is pushed in it is directed upward until it hits the base of the occiput. It is then withdrawn partly and redirected to a point a little lower than the first and in this new direction it will puncture the dura below the base of the skull. As these punctures are being done it is well to withdraw the stylet from the needle at intervals to see whether the subarachnoid space has been reached and whether cerebrospinal fluid can be obtained. Ordinarily as the dura is penetrated there is an unmistakable sensation of a give to indicate it. In doing a cisternal puncture it is not wise to penetrate deeper than 5.5 or 6 cm. in the ordinary person and the needle should be marked so that this point will be known. Ventricular puncture is made through trephine openings in the skull and with a large blunt needle marked off in centimeters which is inserted into the ventricles through the brain substance. It is a surgical procedure which ordinarily should not be carried out unless one is in a position to deal with whatever type of lesion may exist.

While ventricular puncture has its limitations in ordinary surroundings lumbar and cisternal punctures have their contraindications. They should be carried out with caution if a brain tumor is suspected and ordinarily should not be done at all if there is papilledema indicating increased intracranial pressure or the suspicion of a tumor in the posterior fossa. The reason is that if pressure is released below by removal of fluid and if a lesion in the posterior fossa interferes with the escape of fluid from the intracranial cavity the medulla and cerebellum are likely to be pushed down into the foramen magnum and become compressed and edematous and death may ensue. Such pressure cones or cerebral herniations with distinct grooves in them from pressure of the edges of the foramen magnum can be seen on

postmortem examination. Following lumbar puncture patients may complain of headache and even vomiting and a stiff neck. Ordinarily this can be prevented by keeping the patient in bed for twenty four hours after the puncture. While it is not certain, the cause is probably a continuing leak of cerebrospinal fluid through the hole made in the dura. Forcing fluids, the use of pitressin, as an antidiuretic, and the administration of hypotonic saline solution intravenously, may all be used to overcome the symptoms but the most important thing is to maintain a recumbent position. These symptoms may last as long as five or seven days, although ordinarily they pass off much more quickly.

Normally the cerebrospinal fluid is under a pressure of 80 to 170 mm with the patient lying on his side and the occiput and lumbar puncture needle in the same horizontal plane. This pressure can be determined easily by connecting an Ayer manometer to the lumbar puncture needle by means of a three way stopcock. The manometer is a hollow glass tube graduated

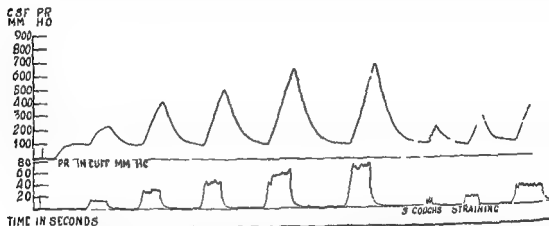


FIG. 384.—A normal tracing of changes in cerebrospinal fluid pressure (left) and pressure of the jugular vein (right) in the lumbar subarachnoid space. The top tracing and pressure applied by means of a sphygmomanometer cuff about the neck (shown in the lower tracing). The time is recorded in seconds at the bottom. Application of pressure to the jugular vein results in a rapid and free rise in spinal fluid pressure. Release of pressure on the jugular vein causes a rapid free return to original spinal fluid pressure. Coughing and straining also raise intracranial pressure. (Courtesy of Drs. W. T. Grant and W. A. Cone.)

in millimeters and when the spinal fluid, which has flowed into the tube, reaches a constant level the pressure can be read off in terms of millimeters of spinal fluid. The fluid level, however, is not at rest because oscillations are transmitted to it coincident with each heartbeat and respiration. This pressure is increased frequently in diseases of the nervous system and this is discussed further in a consideration of the individual diseases.

It is a well known law of physics that pressure applied to a fluid medium is transmitted equally in all directions through it. This applies to the cerebrospinal fluid circulation and forms the basis of the Queckenstedt test which is used to determine whether or not there is a block in that circulation. Compression of the jugular veins causes blood to dam back within the skull and this raises intracranial pressure. The increase in pressure is transmitted throughout the cerebrospinal fluid and can be measured in the lumbar subarachnoid

space by means of a lumbar puncture needle and manometer. Normally compression of each internal jugular vein separately, or both together, causes a rapid rise in spinal fluid pressure and, when the compression is released the spinal fluid pressure quickly returns to normal. The maximum change should occur within 10 to 20 seconds of the application or release of pressure. Compression of the jugular veins on the two sides separately need not result in equal increases in spinal fluid pressure but bilateral compression causes a greater increase than unilateral compression. In addition to compression of the veins other procedures will increase cerebrospinal fluid pressure. Coughing and abdominal straining will do so by increasing the intrathoracic and intraabdominal pressures and impeding venous drainage from the vertebral canal.

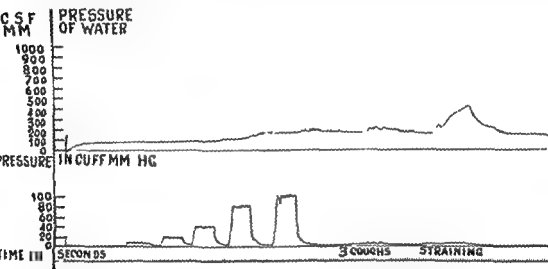


Fig. 39.—Tracing in Fig. 394 but in a complete block (Courtesy of Dr. W. T. Grant and W. A. Cone)

Grant and Cone have recently modified the Queckenstedt test in an effort to make it more graphic and exact and to make several determinations at different times comparable to one another. They apply pressure about the neck by means of a sphygmomanometer cuff and they record on a kymograph the pressure within the cuff and the pressure of spinal fluid in the lumbar region together with a time tracing. Two of their records are shown here. Fig. 394 is a normal tracing. Successively greater cuff pressures applied about the neck cause successively greater rises in spinal fluid pressure. The response is rapid and the recovery is rapid. Coughing and straining also cause coincident increases in pressure. Since pressure is transmitted equally throughout the fluid medium the same observations normally can be made on cistern puncture and on lumbar puncture. If the two are carried out at the same time equal and practically simultaneous changes should be found in each.

If a complete block occurs in the cerebrospinal fluid system the changes in pressure will not be transmitted beyond the block. This is shown well in Fig. 395 in which inflation of the cuff is not followed by a rise in cerebrospinal

fluid pressure If a partial block occurs, the changes in pressure will be less pronounced and less rapid than normal and the return to normal, after the release of jugular compression, will not be complete The reason for this last observation is that the increased intracranial pressure may be sufficient to force some fluid past the block, but the pressure within the sac distal to the block is not sufficient to force the fluid back again

Not only will this test show the presence of a block, but it can also be used to show the location of the block If compression of the internal jugular vein on one side is followed by a normal response while on the opposite side there is no response, the block is apparently not in the cerebrospinal fluid circulation but in the venous circulation itself This occurs in thrombosis of the lateral sinus in which compression of the internal jugular vein, on the same side, causes no increase in the venous block which already exists and so no change in intracranial pressure With a block in the vertebral canal such as frequently occurs with cord tumors, a puncture of the cisterna magna will show normal pressure reactions while a lumbar puncture will show evidence of block If the block is high up, in the cervical region, increases in pressure induced by coughing and straining will both be transmitted to the lumbar puncture needle If it is lower, the changes on coughing will not be demonstrable while those on straining will remain, though they may be reduced With a lesion in the lower thoracic or lumbar region both will be abolished It is sometimes possible, in cases of cauda equina lesions, to insert needles both above and below the lesion and the same comparative studies can be carried out in the two

*Normal spinal fluid is clear and colorless and contains less than 9 white blood cells per cubic millimeter It has a total protein content that varies from 5 to 35 or 40 mg per cent, depending on its source, and which usually averages about 25 mg per cent The sugar content varies from 50 to 85 mg per cent and the chlorides, as sodium chloride, 700 to 750 mg per cent All these characteristics undergo changes in disease and these are recorded in the symptomatology of the individual diseases*

### X ray Examinations

By means of x ray examinations a great deal of information can be obtained which forms an important part of the study of many neurological cases The skull and vertebral column like other bony structures, impede the passage of the rays and so can be photographed clearly Their different parts such as the sella turcica the mastoid air cells the accessory nasal sinuses the suture lines the intervertebral discs etc can all be well differentiated In addition, by special posturing various structures such as the optic foramen and the internal auditory meatus can be brought into view and deviations from the normal may be seen The different structures of the brain and cord on the contrary can ordinarily not be seen unless special measures are taken to visualize them

The skull may show deviations from the normal shape and size, its sutures may be prematurely closed or their closure may be delayed because of increase in intracranial pressure Fusion of the bones of the two sides may be incom

plete and cranium bifidum or spina bifida may be apparent. By a study of the adult skull and a comparison of the growth of its various parts and of the structures of the face, it may be possible to determine the state of activity which the endocrine glands concerned in growth have exercised during different age periods. Changes in the continuity of the bones and in their relationship to one another follow fractures or dislocations or a combination of the two. The normal contour and density of the bones of the skull and vertebral column may be altered by disease within themselves or disease involving them from without. Erosions occur from tumors within the skull and also from the pressure of meningeal tumors against the inner table of the



Fig. 396.—Marked pre- or sub-arachnoidal atrophy of the skull from increased intracranial pressure. Note that the pattern of this atrophy is a faithful print of that of the brain surface.

skull. These erosions may be single or multiple. When intracranial pressure is increased generally over a long period of time the pressure of the brain against the skull may gradually cause an atrophy of the latter. This atrophy will be present where the convolutions have pressed against the skull but not opposite the sulci where no pressure has been exerted. The resulting appearance of the atrophy of the bone will be that of an impression of the surface of the brain (fig. 396). Such an appearance, though of lesser degree than that illustrated, may be seen normally in the skulls of children without any increase in intracranial pressure. In the same way tumors within the vertebral canal may cause some erosion of the bodies of the vertebrae or erosion of the pedicles and widening of the interpedicular spaces.

Erosion of the sella turcica by pituitary tumors is well known, but such erosion may also occur with suprasellar tumors at a distance. In the same way auditory nerve tumors may erode the internal auditory meatus and meningeal tumors, the optic foramen. It is important that all parts of the skull be examined minutely for erosions, proliferations, calcifications, and increased vascularity. Proliferative changes may occur side by side with other changes, such as erosion and deposition of calcium. It may be due to disease of the bones, as in Paget's disease, or secondary involvement of the bone as in meningeal fibroblastoma. In the latter the normal vascular markings are frequently increased in the location of the tumor.



Fig. 397.—The calcified pineal gland can be seen and behind it and very slightly above are the shadows of the choroid plexus of each side.

Ordinarily the different parts of the brain and spinal cord cannot be differentiated in an x-ray film. Normal calcifications sometimes occur which may, however, give a great deal of information about the intracranial contents. In adult life the pineal gland is often calcified and this can be seen both in anteroposterior and lateral views (Fig. 397). Deviation from its normal position may occur in tumors of the brain. Occasionally calcification may occur, presumably without pathological significance in the choroid plexus; this is also shown in Fig. 397. Areas of calcification in the falx and in the petroclinoid ligament just behind the sella turcica also occur without obvious disability. These are calcifications which are regarded as normal but calcification may occur in connection with pathological lesions, such as old

abscesses and some tumors and hemorrhages. In addition, the intracranial portion of the internal carotid artery may occasionally show calcification on x ray examination.

In 1918 Dandy introduced a method of x ray examination which has been of inestimable value since. As stated above, the intracranial contents cannot be differentiated from one another. Brain substance and the cerebrospinal fluid within the subarachnoid space and the ventricles cast no distinctive shadows, as they impede the passage of x rays to the same extent. Dandy

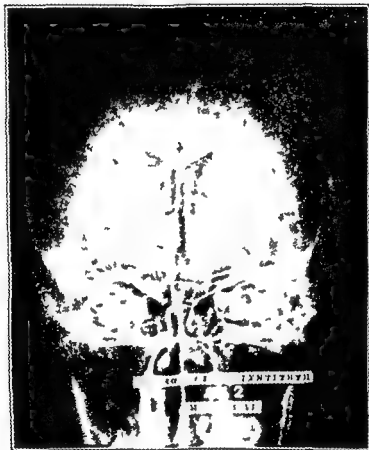


Fig. 298.—Anteroposterior view of skull. Note the butterfly-like configuration of the lateral ventricles. Below them of the third ventricle and the atelectic filling of the subarachnoid space.

found that if the cerebrospinal fluid is replaced by air, the air containing spaces will then be differentiated on an x ray film from the surrounding structures. The exchange can be made by means of a needle inserted into the ventricular system through a trephine opening (ventriculography) or by means of a needle inserted into the lumbar subarachnoid space (encephalography). Ventriculography has the same restrictions as ventricular puncture; it is a surgical procedure which should be carried out only if facilities exist to immediately deal with whatever type of lesion is found. Encephalography has the same contraindications as lumbar puncture, it should not be

Erosion of the sella turcica by pituitary tumors is well known, but such erosion may also occur with suprasellar tumors at a distance. In the same way auditory nerve tumors may erode the internal auditory meatus and meningeal tumors, the optic foramen. It is important that all parts of the skull be examined minutely for erosions, proliferations, calcifications, and increased vascularity. Proliferative changes may occur side by side with other changes, such as erosion and deposition of calcium. It may be due to disease of the bones, as in Paget's disease, or secondary involvement of the bone as in meningeal fibroblastoma. In the latter the normal vascular markings are frequently increased in the location of the tumor.



FIG. 397.—The calcified pineal gland can be seen and behind it and very slightly above are the shadows of the choroid plexus of each side.

Ordinarily the different parts of the brain and spinal cord cannot be differentiated in an x-ray film. Normal calcifications sometimes occur which may, however, give a great deal of information about the intracranial contents. In adult life the pineal gland is often calcified and this can be seen both in interoposterior and lateral views (Fig. 397). Deviation from its normal position may occur in tumors of the brain. Occasionally calcification may occur, presumably without pathological significance in the choroid plexus; this is also shown in Fig. 397. Areas of calcification in the falx and in the petroclmoid ligament just behind the sella turcica, also occur without obvious disability. These are calcifications which are regarded as normal but calcification may occur in connection with pathological lesions, such as old



Normally the ventricular system lies in the midline (figs 398 and 399). Distortion, filling defects or displacements of it are pathological conditions which will show up in the encephalogram. The abnormality may exist throughout the ventricles or it may be limited to one portion.

Tumors of the brain displace the system to the opposite side by pushing it away. They frequently, also, collapse the homolateral ventricle, or a portion of it and dilate the contralateral ventricle. Encroachment may be made on any part of the lateral ventricles, third ventricle or fourth ventricle. If the tumor is in the posterior fossa and interferes with drainage of cerebrospinal fluid it will dilate the entire ventricular system proximal to it. In such



Fig. 400.—Outline of the vascular tree during the injection of thorotrast. Note that the anterior and middle cerebral arteries lead to a circumscribed area of increased vascularity. This was in the region of a cerebral cicatrix.

In case it may not be possible to fill the ventricles from below, but only by means of direct introduction of air into them through trephine openings. Contracting lesions instead of pushing the brain away exert a traction upon it and distortion of the ventricles may again occur. In such a case however displacement will be toward the side of the lesion and not away from it. It is frequently found that the part of the ventricle nearest the lesion is pulled out of position. On the surface of the brain opposite this pull air may collect in such a quantity as to indicate an area of atrophy or a cystlike collection in the subarachnoid space.

By the injection of thorotrast, a thorium salt into the internal carotid artery the vascular tree of the brain can be outlined. In order that proper

done when a posterior fossa tumor is suspected or when there is papilledema suggesting the presence of tumor of the brain

Encephalography can be done with the patient in an erect sitting position or lying on his side. It is possible by posturing the patient to direct most of the air to the site desired. Ordinarily when this procedure is carried out as a diagnostic test, it is desired to fill both the ventricles and subarachnoid space and it is done with the patient erect. At other times the aim is to direct the air chiefly to the subarachnoid space and in this case the patient is made to lie on his side with that part of the head uppermost where filling should be most complete. This particular posturing is used chiefly in cases of subarachnoid



Fig. 399.—A normal encephalogram. Lateral view of the ventricles and subarachnoid space

adhesions and posttraumatic headache. The exchange of cerebrospinal fluid and air or oxygen is carried out fractionally and slowly and an effort is made to keep the cerebrospinal fluid pressure as nearly constant as possible. In this way it is possible to withdraw as much as 100 to 120 cc of spinal fluid and inject the same or a little greater amount of air.

After the injection x rays are taken in anteroposterior, posteroanterior and right and left lateral positions. By gently manipulating the head and posturing it, air can be directed into the various parts of the ventricular system for photography. Stereoscopic plates are taken so that three dimensional studies can be made. In addition by placing the brow or the occiput uppermost air can be directed to the anterior or the posterior portions of the system.

**x rays** It can be introduced into the cisterna magna and allowed to descend in the subarachnoid space by gravity. It is also sometimes given into the lumbar subarachnoid space and the patient is then tilted with the head downward so that gravity will carry the substance higher into the vertebral canal. In the presence of an obstructing lesion such as a tumor or adhesions the substance will be held up by the obstruction and the level of this arrest can be determined by x ray examination. Fig. 401 was taken after the injection of lipiodol, both into the cisterna magna and into the lumbar subarachnoid space and the x ray film shows how well outlined are the upper and lower borders of the obstructing lesion. Recently a compound named pantopaque has been introduced which is supposed to be less toxic, has less local irritating effects and can be more easily removed in whole or in part. If the responses to the Queckenstedt test are normal it is unnecessary to inject these substances as there is apparently no obstruction to the flow of cerebrospinal fluid. If however the responses to jugular compression indicate that there is a block and if clinically the level of this block cannot be determined then they can be used to advantage.

## DISEASES OF THE NERVOUS SYSTEM

### Diseases Due to Prenatal Influences

#### Dysplasia

Defects in growth may occur at any time during the development of the nervous system. If this happens early or if the structural defect is a severe one it may be incompatible with life or result in the formation of a monster. The defect may take the form of absence of parts, even of the cerebral hemispheres (anencephaly) or spinal cord (amelia). The failure of development may be more restricted to a single structure or unit such as the corpus callosum, certain cranial nerve nuclei or motor or sensory pathways. A part even though present may fail to attain its proper growth. The brain may be small (microcephaly) and enclosed in a small skull. The deficient growth may be limited to one half or to the gyri of the cerebral hemispheres (microgyria). It has been found that with microgyria in one cerebral hemisphere there is usually also imperfect growth in other regions of the nervous system such as the opposite cerebellar hemisphere. Failure of development of parts based upon their position in the phylogenetic scale has been described and Brouwer has reported atrophy of the neocerebellum and of the neo olives with preservation of the phylogenetically older parts of both.

The reverse condition is shown in macrogyria in which the brain is considerably larger than normal. Another abnormally excessive type of growth is reduplication of the lower part of the spinal cord in which an apparently normal cord lies side by side with a smaller replica. Heterotopia is a condition in which certain structures or cellular groups become displaced from their normal positions during development such as cellular groups normally present in grey matter being displaced into white matter.

With these various defects in growth the symptomatology may vary greatly. In some cases a live birth is impossible. In others monsters are born who live but for a short time. On the other hand it is surprising what de-

pictures be obtained, a special routine is necessary. X ray exposures must be made at the most frequently possible intervals during the administration of the substance. Thorium, like other metals, impedes the passage of x rays and so the vessels containing this substance show up sharply on the film. Fig. 400 shows the result of such a method. By this means abnormalities in the



Fig. 401.—Upper and lower borders of a tumor of the spinal cord outlined by means of lipiodol

blood vessels themselves such as aneurysms and abnormal vascularization in the region of other lesions become apparent. This procedure should be carried out with caution, as thorotrast is an irritant in perivascular tissues and is also a radioactive substance (see pages 700 and 1114).

For some years lipiodol (iodine in vegetable oil) was used to locate blocks in the spinal subarachnoid space. This substance is also opaque to



velopmental defects may occur with little or no symptomatology, much less in fact than if a comparable condition had been produced by disease. Mentality is frequently retarded in these conditions and epileptic attacks are common symptoms. The diagnosis depends upon the history of the case and also upon the appearance of the patient if this is at all characteristic. These conditions being developmental defects are not amenable to treatment, but if the resulting disability is slight, it is possible, by training and education, to bring about improvement in the individual's capacity.

### Cranium Bifidum and Spina Bifida

**Definition**—Cranium bifidum and spina bifida are defects resulting from imperfect closure of the bony structures of the skull and vertebral column in the midline. It occurs most frequently in the vertebral column, as spina bifida.



Fig. 40.—Spina bifida with meningocele in the cervical region.

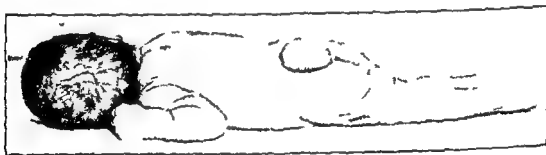


Fig. 403.—Spina bifida with meningocele in the lumbosacral region.

and especially in the cervical (Fig. 402) and lumbosacral (Fig. 403) regions as these are the last to unite. Cranium bifidum also usually occurs posteriorly and rarely in the frontal region. The defects may be apparent or they may be so slight as to escape notice, in which case they are called occult. In the vertebral column the imperfect fusion is almost always posteriorly, but very rarely it occurs anteriorly as well. Through the defect in the bone meninges may protrude and form a sac covered by thin tissue paper like skin over the region of the defect. This condition is known as a meningocele. Within the meningocele traction may be made on nervous structures which become ad-

**Etiology**—The etiology is unknown. It is possibly due to a disturbance in lipid metabolism. It has been described in association with Niemann Pick disease (page 578) and the same type of cellular changes has been found in the two conditions.

**Symptoms**—The ordinary form of this disease is the infantile in which symptoms first appear about the age of three or four months. There are progressive apathy and a gradually increasing muscular weakness and flaccidity first noticed in an inability to hold up the head. Vision becomes impaired and optic atrophy and blindness follow. The cherry red spot which is characteristic of this disease is seen in the macula lutea. Weakness spreads throughout the body, emaciation follows, the reflexes become increased, and spasms and convulsions may occur. During the course of the illness the muscles may be spastic for a time. The mental enfeeblement is progressive to the point of idiocy. Death usually occurs within two years.

A late infantile type (Bielchowsky Jansky type) also exists in which symptoms first appear about the age of three or four years and in which the patient may live about four years. There is also a juvenile type (Spielmeyer Vogt type) beginning between the ages of seven to twelve years running a longer course not associated with macular changes and occurring in Gentiles.

**Pathology**—This disease is characterized by widespread cellular changes. The nerve cells become swollen and pear shaped, the nucleus is pushed to the side and the cytoplasm becomes a homogeneous lipid substance which bulges the cell membrane. The neurofibrils occupy the periphery of the cell body and around the nucleus there may be remains of Nissl substance.

**Prognosis**—The disease progresses until death occurs. Its duration may vary from one to eight or ten years. The earlier the onset the shorter the duration.

**Treatment**—There is no known treatment.

### *Pelzaens Merzbacher Disease*

**Synonym**—Aplasia axialis extracorticalis congenita

**Definition**—A rare congenital and familial disease characterized by diffuse demyelination in the brain.

**Etiology**—This disease may be a chronic type of diffuse sclerosis and it is possible that it is an acquired and not a congenital disease.

**Symptoms**—There may be an acute or subacute onset beginning at the age of one to five years and then followed by a chronic course. Ordinarily there are ataxia and spasticity of the legs, nystagmus, slowness of speech and mental retardation. There may be optic atrophy and abnormal movements either coarse tremors or choreiform movements.

**Pathological Anatomy**—There is diffuse demyelination of the white matter of the brain without inflammatory reaction but with extensive glial proliferation.

### *Tuberose Sclerosis*

**Synonyms**—Epiloia, tuberous sclerosis

**Definition**—A disease manifested by adenoma sebaceum, intellectual retardation and epilepsy.

present and epilepsy occurs frequently in these individuals. In marked cases of mental deficiency the defect becomes apparent early in the life of the child, while in borderline cases it may pass practically unnoticed and the individual may be self supporting throughout his life. By means of standardized tests, such as the Binet-Simon tests, the intelligence quotient, the ratio of mental age to chronological age can be determined. Sometimes stigmata, such as disproportionate features, may be apparent. Occasionally psychotic symptoms occur on a basis of mental deficiency and sometimes also stereotyped movements appear. Because of the low intellectual level and judgment, the patient may require watching to be kept out of trouble.

**Treatment**—The higher grade mental defectives may frequently be trained in some simple occupation which will make them self supporting. Lower grades are not amenable to such training and may require institutional care because of their dependence, or behavior disorders, or because of epilepsy which may be associated.

### Mongolian Idiocy

**Synonym**—Mongolism

**Definition**—Idiocy in association with mongoloid features (eyes slant downward and inward, the nose is broad and flat, the tongue thick and fissured) a small skull and sometimes other congenital anomalies.

**Etiology**—This is unknown. The condition has been attributed to the age of the parents and the number of children previously born to them, but these are doubtful etiological factors. Mongolian idiocy has been described in identical twins which indicates a determining factor in the germ plasma. The presence of mongolism in only one of dissimilar twins supports this. Mongolian idiots are frequently born to people of superior intelligence.

**Symptoms**—The striking feature of this condition is the mongolian facies and this, in conjunction with the idiocy and the small skull flattened both in front and behind is usually sufficient to establish the diagnosis. The chief differentiation that must be made is from cretinism (p. 937). The presence of congenital cardiac lesions, a protuberant abdomen and large flat hands and feet aid in the diagnosis. The intellectual defect is a marked one.

**Pathological Anatomy**—The brain is small and there is an aplasia of cells, cell layers and sometimes entire gyri.

**Treatment**—There is no treatment for this condition. Usually the individual dies in infancy or soon after although occasionally one has lived to adult life.

### Amaurotic Family Idiocy

**Synonym**—Tay-Sachs disease

**Definition**—A disease occurring in infancy and characterized by progressive mental enfeeblement, muscular weakness, optic atrophy and blindness and the occurrence of a cherry red spot in the macula of the retina.

**Incidence**—This is a familial disease which is almost exclusively confined to Jews and which usually affects more than one child in the family.



defect may be more marked in the Rolandic area where the nerve cells are fewer in number, the cell layers poorly developed and there is a hyperplasia of neuroglia cells and fibers

**Prognosis**—The disability may remain stationary or show a slight, gradual improvement. Some cases progress. In itself this condition does not threaten life but like so many other diseases with this degree of incapacity the individual is less resistant to intercurrent disease.

**Treatment**—The treatment consists of education and training and orthopedic measures to overcome or prevent deformities. In those cases which tend to improve and in which there is no great mental retardation, much can be done by proper exercises. Massage and passive movements are also of value.

### Infantile Cerebral Hemiplegia

**Definition**—A hemiplegia present from birth and due to a lesion within the brain.

**Etiology**—Birth trauma or disease affecting the brain before or immediately after birth.

**Symptoms**—This condition, although not a developmental disease, is discussed here because sometimes it is bilateral and may resemble infantile cerebral diplegia. In bilateral infantile hemiplegia however the arms are more involved than the legs signs of other lesions are frequent and mentality is more often impaired than in infantile cerebral diplegia. The symptoms and signs are those of an upper motor neurone lesion, together with whatever pathological signs may be present due to other lesions. Athetoid movements frequently occur in this condition due to involvement of the basal ganglion. In infantile hemiplegias it is not uncommon to find the abdominal reflex preserved. The growth of the involved member or side may be retarded so that it remains throughout life smaller than its opposite. Convulsions later in life are a frequent occurrence.

**Pathological Anatomy**—Since this condition can depend on so many causes the pathology varies. Birth hemorrhages inflammatory diseases, lacerations of the brain all occur. Following them there is often focal atrophy of the area of brain involved with atrophy of nerve cell elements and overgrowth of astrocytes.

**Treatment**—In these cases also training psychotherapy physiotherapy and orthopedic measures are the only methods of treatment but a great deal can be accomplished through assessing and developing their assets rather than by trying only to remedy their liabilities. The treatment of convulsions is discussed in the section on Epilepsy (page 1155).

### Double Athetosis

**Synonym**—État marbre of Oppenheim and C. Vogt.

**Definition**—Athetosis on both sides without pyramidal tract signs occurring as a congenital disease.

**Symptoms**—Increased tone and athetotic movements on the two sides. The movements are more marked in the upper extremities but may occur in

**Etiology**—It is sometimes familial and is due to a congenital abnormality

**Symptoms**—The epileptic attacks begin early and may be major or minor focal or nonfocal. About the age of 4 or 5 years the adenoma sebaceum appears on the face. This spreads over the bridge of the nose and cheeks in the shape of a butterfly. The spots are raised, pink or red, and some are discrete and some confluent. The mental retardation is quite marked. As tumors may appear in other organs of the body, such as the heart or kidney, they may sometimes cause symptoms. The tumors in the brain do not usually cause focal symptoms but may if they grow sufficiently large. Other congenital anomalies, such as hare lip or heart disease, may be present. Blood relations of the patient may show other skin abnormalities.

**Pathological Anatomy**—In the cerebral cortex there are numerous hard, white tumors, varying in size from that of a pea to that of a walnut. These are made up of altered nerve cells and glia cells. The cells in the cortex of the brain show changes and the gyri may show enlargement in places. Tumors or cystic degeneration may be present in other regions of the brain as well especially about the ventricles. Tumors appear elsewhere in the body, in the heart, kidneys, thyroid, skin, retina, etc.

**Treatment**—There is no specific treatment for the condition and the only treatment is symptomatic.

### Infantile Cerebral Diplegia

**Synonyms**—Little's disease, congenital spastic paralysis

**Definition**—A diplegia (paralysis of both sides) which is more marked in or confined to, the legs and is present from birth.

**Etiology**—It is always difficult to decide whether an infantile cerebral diplegia is due to a developmental defect or a birth trauma to the brain. It is probable that either may be the etiological factor or perhaps a combination of the two. Other etiological factors may also be responsible.

**Symptoms**—The symptoms are those of bilateral pyramidal tract involvement and are more marked in the legs and may be confined to them. The disability may escape notice at the time of birth and become recognized because of the slowness of development and the difficulty in learning to walk. The weakness is symmetrical and may be marked or slight with only reflex changes. When very marked the feet are in a position of equino varus and the increased adductor tone crosses one leg over the other so that the patient walks with a 'scissors gait'. In addition to the spastic paralysis there may be cerebellar signs, abnormal movements such as chorea or athetosis (Fig 408), cranial nerve weakness and deformities of the spine. In many cases the mental level is normal and the children are bright and alert. In others there is some degree of mental retardation. Convulsions may also be present. This condition seems to be associated with prematurity in many cases. It has been found in siblings.

**Pathological Anatomy**—There may be gross developmental defects in the brain (microcephaly) or in the convolutions (microgyria) or both. The

defect may be more marked in the Rolandic area where the nerve cells are fewer in number, the cell layers poorly developed and there is a hyperplasia of neuroglia cells and fibers

**Prognosis**—The disability may remain stationary or show a slight gradual improvement. Some cases progress. In itself this condition does not threaten life but like so many other diseases with this degree of incapacity the individual is less resistant to intercurrent disease.

**Treatment**—The treatment consists of education and training and orthopedic measures to overcome or prevent deformities. In those cases which tend to improve, and in which there is no great mental retardation, much can be done by proper exercises. Massage and passive movements are also of value.

### Infantile Cerebral Hemiplegia

**Definition**—A hemiplegia present from birth and due to a lesion within the brain.

**Etiology**—Birth trauma or disease affecting the brain before or immediately after birth.

**Symptoms**—This condition, although not a developmental disease is discussed here because sometimes it is bilateral and may resemble infantile cerebral diplegia. In bilateral infantile hemiplegia, however the arms are more involved than the legs signs of other lesions are frequent and mentality is more often impaired than in infantile cerebral diplegia. The symptoms and signs are those of an upper motor neurone lesion, together with whatever pathological signs may be present due to other lesions. Athetoid movements frequently occur in this condition due to involvement of the basal ganglion. In infantile hemiplegia it is not uncommon to find the abdominal reflex preserved. The growth of the involved member or side may be retarded so that it remains throughout life smaller than its opposite. Convulsions later in life are a frequent occurrence.

**Pathological Anatomy**—Since this condition can depend on so many causes the pathology varies. Birth hemorrhages inflammatory diseases lacerations of the brain all occur. Following them there is often focal atrophy of the area of brain involved with atrophy of nerve cell elements and overgrowth of astrocytes.

**Treatment**—In these cases also training psychotherapy physiotherapy and orthopedic measures are the only methods of treatment but a great deal can be accomplished through assessing and developing their assets rather than by trying only to remedy their liabilities. The treatment of convulsions is discussed in the section on Epilepsy (page 1155).

### Double Athetosis

**Synonym**—*État marbre* of Oppenheim and C. Vogt.

**Definition**—Athetosis on both sides without pyramidal tract signs occurring as a congenital disease.

**Symptoms**—Increased tone and athetotic movements on the two sides. The movements are more marked in the upper extremities but may occur in

**Etiology**—It is sometimes familial and is due to a congenital abnormality.

**Symptoms**—The epileptic attacks begin early and may be major or minor focal or nonfocal. About the age of 4 or 5 years the adenoma sebaceum appears on the face. This spreads over the bridge of the nose and cheeks in the shape of a butterfly. The spots are raised, pink or red, and some are discrete and some confluent. The mental retardation is quite marked. As tumors may appear in other organs of the body, such as the heart or kidney, they may sometimes cause symptoms. The tumors in the brain do not usually cause focal symptoms but may if they grow sufficiently large. Other congenital anomalies such as hare lip or heart disease, may be present. Blood relations of the patient may show other skin abnormalities.

**Pathological Anatomy**—In the cerebral cortex there are numerous hard, white tumors, varying in size from that of a pea to that of a walnut. These are made up of altered nerve cells and glia cells. The cells in the cortex of the brain show changes and the gyri may show enlargement in places. Tumors or cystic degeneration may be present in other regions of the brain as well especially about the ventricles. Tumors appear elsewhere in the body, in the heart, kidneys, thyroid, skin, retina, etc.

**Treatment**—There is no specific treatment for the condition and the only treatment is symptomatic.

### Infantile Cerebral Diplegia

**Synonyms**—Little's disease, congenital spastic paralysis.

**Definition**—A diplegia (paralysis of both sides) which is more marked in, or confined to, the legs and is present from birth.

**Etiology**—It is always difficult to decide whether an infantile cerebral diplegia is due to a developmental defect or a birth trauma to the brain. It is probable that either may be the etiological factor or perhaps a combination of the two. Other etiological factors may also be responsible.

**Symptoms**—The symptoms are those of bilateral pyramidal tract involvement and are more marked in the legs and may be confined to them. The disability may escape notice at the time of birth and become recognized because of the slowness of development and the difficulty in learning to walk. The weakness is symmetrical and may be marked or slight with only reflex changes. When very marked the feet are in a position of equino varus and the increased adductor tone crosses one leg over the other so that the patient walks with a scissors gait. In addition to the spastic paralysis, there may be cerebellar signs, abnormal movements such as chorea or athetosis (Fig 408), cranial nerve weakness and deformities of the spine. In many cases the mental level is normal and the children are bright and alert. In others there is some degree of mental retardation. Convulsions may also be present. This condition seems to be associated with prematurity in many cases. It has been found in siblings.

**Pathological Anatomy**—There may be gross developmental defects in the brain (microcephaly) or in the convolutions (microgyria), or both. The

the pyramidal tracts and the spinocerebellar tracts, with a secondary gliosis

**Prognosis**—The disease may remain stationary but is usually very slowly progressive so that it may result in complete incapacity

**Treatment**—There is no specific treatment

### Hereditary Cerebellar Ataxia

**Synonym**—Marie's ataxia

**Definition**—Another type of hereditary ataxia in which the manifestations are more truly cerebellar and in which the skeletal deformities are not present. It is sometimes very difficult to differentiate this from Friedreich's ataxia, as well as from other conditions described below, and they probably represent the same type of abiotrophy with more restricted or widespread involvement in the different cases

**Symptoms**—These closely resemble the symptoms of Friedreich's ataxia as far as ataxia, nystagmus and speech disturbances are concerned. The onset is later than in Friedreich's disease and there is no scoliosis nor deformity of the foot. The tendon jerks are increased and there is a bilateral Babinski sign. In addition there may be ocular manifestations such as optic atrophy or paralysis of external ocular muscles. Special forms have been described by Sanger Brown and by Dejerine and Thomas. The Sanger Brown type comes on later and the pathological changes are almost confined to the spinocerebellar tracts. The posterior columns may be involved but the corticospinal tracts usually escape. Ataxia, speech disturbance, spontaneous movements, ocular palsies and optic atrophy occur. The Dejerine Thomas type has a widespread involvement of the cerebellum and pons and begins in middle life.

**Pathological Anatomy**—As in Friedreich's ataxia there is an atrophy of nervous elements and a replacement with glial scar. There is degeneration of the spinocerebellar tracts, the cerebellum and the pyramidal tracts.

### Hereditary Spastic Paraplegia

**Definition**—A rare hereditary and familial disease manifested by a slow progressive paralysis of the legs beginning at the age of five or seven and increasing for many years. The paralysis is of an upper motor neurone type and shows the characteristic signs. Contracture may occur and the disease may spread to the upper limbs and cranial nerves.

**Etiology**—Unknown, regarded as an abiotrophy.

**Pathological Anatomy**—There is agenesis of the spinal cord and degeneration of the pyramidal tracts. In late cases the posterior columns and direct spinocerebellar tracts may also be involved.

### Family Periodic Paralysis

**Definition**—A rare familial disease manifested by recurring spells of flaccid paralysis.

**Etiology**—Unknown. This disease may skip a generation or may involve several members of the same family.

**Symptoms**—In an otherwise healthy individual attacks of paralysis occur usually during sleep which involve different muscle groups and more than

the toes as well. Athetosis is a frequent accompaniment of diseases affecting the pyramidal tract before, during, or immediately after birth, but in addition it may occur without pyramidal tract involvement.

**Pathological Anatomy**—The lenticular nuclei have the appearance of marble and for that reason the condition has been called *état marbre*. There are areas of atrophied ganglion cells and a resulting sclerosis in the caudate nucleus and the putamen of the lenticular nucleus. The globus pallidus is less involved.

**Treatment**—There is no specific treatment for this condition. Symptomatic treatment with stramonium and hyoscine will probably not help greatly. The entire question of the treatment of extrapyramidal motor diseases has been stimulated by the study of surgical section of extrapyramidal pathways in the anteromedian part of the cord as introduced by Tracy Putnam.

### Friedreich's Ataxia

**Synonym**—Hereditary ataxia

**Definition**—This is one of a group of hereditary ataxias which merge into one another and which frequently cannot be positively differentiated from one another. There is degeneration of the posterior columns of the spinal cord, the pyramidal tracts, and the spinocerebellar pathways.

**Etiology**—The disease is hereditary and frequently occurs in siblings. Its ultimate cause is unknown, but it has been grouped among the abiotrophies or diseases due to inability of certain parts of the nervous system to develop fully to functional maturity.

**Symptoms**—The disease first manifests itself about the time of puberty. Ataxia or incoordination appears first in the lower extremities and gradually extends to involve the whole body. This ataxia may be manifested on movement or at rest. Walking is interfered with; the patient walks on a broad base and sways as he does so. Dysmetria and dyssynergia are present in movements of the hands and arms. Movements are clumsily carried out. Spontaneous irregular movements of the head and shoulders and extended limbs occur. Tonicity and reflexes will depend upon the relative involvement of the posterior columns and pyramidal tracts. There may be hypotonia or spasticity and the tendon reflexes may be absent or increased. Frequently the knee jerks are increased and the ankle jerks absent. The plantar response is extension. Nystagmus and speech disturbances are characteristic. The speech becomes monotonous and slurred or scanning or staccato and some times explosive. Skeletal deformities occur such as scoliosis and a typical deformity of the foot which is shortened, has a high exaggerated longitudinal arch and hyperextended toes so that the big toe may assume the position which is ordinarily shown in a Babinski response. Sensory changes are not common although impairment of position and muscle sense may occur. The disease may be fully manifested in one member of a family and only some of its symptoms such as the deformity of the foot may appear in others.

**Pathological Anatomy**—The spinal cord is small and the cerebellum also may be smaller than normal. There is degeneration in the posterior columns

### Progressive Lenticular Degeneration

**Synonyms**—Wilson's disease hepato-lenticular degeneration

**Definition**—A familial disease manifested by rigidity, involuntary movements degeneration of the lenticular nuclei and cirrhosis of the liver

**Etiology**—Unknown considered perhaps to be toxic in origin

**Symptoms**—The onset is during the second decade of life. The course may be acute, subacute or chronic. There is a rigidity which may lead to contractures. Abnormal movements such as tremor, choreic or athetotic movements are present. There are no pyramidal tract signs and no true paralysis sensory loss or reflex changes. Because of the spasticity and movements voluntary motion is impaired, and this causes difficulty in swallowing and talking as well as in the use of the limbs. There is often an emotional disturbance, and late in the illness there may be some deterioration. In a few cases a ring of greenish brown pigmentation has been found around the cornea. There is marked cirrhosis of the liver.

**Pathological Anatomy**—There is degeneration in the lenticular and caudate nuclei. This may spread from these nuclei into surrounding structures and cavitation may occur. The cirrhosis of the liver is a mixed type.

**Prognosis**—In the acute cases death may ensue within a few months. Other cases last for several years before death occurs.

**Treatment**—There is no known treatment.

### Pseudosclerosis

**Synonym**—Westphal's disease

**Definition**—Although this disease was first regarded as a separate entity it is now considered a form of progressive lenticular degeneration.

**Symptoms**—This disease begins in young people with tremor of one limb which gradually spreads to involve the entire body. There is muscular rigidity movements are slow and the face expressionless and masklike. Personality changes and dementia occur. These conditions exhibit the signs of extrapyramidal motor system disease with increase in tonicity, the presence of abnormal involuntary movements, the slowness and stiffness of voluntary movement and the masklike face.

**Pathological Anatomy**—The pathology is like that of Wilson's disease, with degeneration of the lenticular nucleus and glial proliferation. The changes in pseudosclerosis are not as gross as those in Wilson's disease and in addition the cerebral cortex may be involved.

**Prognosis**—Death usually occurs within a few years.

**Treatment**—There is no treatment.

### Amyotonia Congenita

**Synonyms**—Myatonia congenita, Oppenheim's disease

**Definition**—A condition of extreme muscular hypotonia without true paralysis.

**Etiology**—This is considered to be a congenital disease of the lower motor neurones and the muscles.

one extremity at a time. The paralysis may spread to involve all the limbs and sometimes the trunk musculature. The signs are those of a flaccid, lower motor neurone paralysis with loss of tendon jerks and abolition of galvanic and faradic excitability. The cranial nerves are rarely involved. There are sometimes electrocardiographic changes, bradycardia and cardiac dilatation during an attack. It begins in early life, lasts many years and the individual attacks last from one hour to several days.

**Pathological Anatomy**—This is unknown and cannot be demonstrated even on post mortem examination.

**Prognosis**—The condition lasts for many years. Occasionally death may occur in an attack. Biernard and Polak Daniels have recently described this condition passing over into a permanent muscular weakness.

**Treatment**—Recently it has been shown that these attacks are associated with marked decrease in the serum potassium and that the administration of potassium at the onset of an attack, either by mouth or intravenously, may cause the paralysis to disappear or to improve within a short time. The daily administration of potassium chloride, 4 to 6 grams may prevent the attacks from occurring.

### Huntington's Chorea

**Synonym**—Hereditary chorea.

**Definition**—An hereditary disease manifested by chorea, beginning in middle age and progressive dementia.

**Etiology**—This is a true hereditary disease which is more common in America than in Europe. It has been possible to trace large numbers of these cases back to the original carriers. Davenport in studying the heredity of nearly 1000 cases found that practically all could be traced back to some half dozen individuals including three brothers who came to America in the seventeenth century. Both sexes transmit the disease, but those who remain free of it will not transmit it. Owing to its late onset an individual may marry and only later develop the symptoms.

**Symptoms**—The onset is usually about the age of thirty to forty five years. The progress is slow and insidious and it may begin with the involuntary movements or the mental change. The movements may begin in the face or upper limbs but gradually involve the entire body. They are rapid, jerky, twisting irregular choreic movements which cause grimacing, dysarthria and difficulty in walking and in using the arms. The mental change is a gradual deterioration sometimes with depression, delusions and irritability. Suicide is not uncommon among these patients.

**Pathological Anatomy**—There is atrophy of the brain especially of the frontal lobes and the corpus striatum (caudate and lenticular nuclei). The ganglion cells in these regions are atrophied and reduced in number. There is a glial proliferation in these atrophied areas.

**Prognosis**—The prognosis is bad as the disease is chronic and progressive and usually terminates fatally in ten to fifteen years.

**Treatment**—The only treatment of the disease is institutional care. Sedatives may help.



### Myotonia Congenita

**Synonym**—Thomsen's disease Although the name is somewhat the same, this condition is not related to myatonia congenita. Myotonia is an increased tonus of muscles, myatonia or amyotonia is a lack of tone or an atony of muscles.

**Definition**—An hereditary disease manifested by difficulty in starting contraction and relaxation of muscles and consequently a slowness in changing the posture of muscles and in initiating movements.

**Etiology**—The disease is hereditary and has been described in seven generations of Thomsen's own family.

**Symptoms**—The symptoms first become apparent in childhood although in some cases they are not noticed until adult life. When an attempt is made to carry out a voluntary movement it is difficult to overcome the tonus of muscles and so to start the movement. Thus if the patient starts to fall, he cannot bring muscles into action to right himself sufficiently quickly, in walking the first few steps are taken slowly and with great difficulty then the muscles loosen up and the patient can walk well on being told to grasp something, the patient cannot do so until an interval has elapsed. In the same way relaxation is difficult. If the patient has something in his grasp and is told to let go he cannot do so immediately but an appreciable interval passes before he can relax his grip. Response to tapping the muscle and electrical stimulation of it show the same phenomena the response is delayed and slow and prolonged. There is no wasting of muscles in fact they may be enlarged and reflexes and sensation are normal. The disease varies in severity and in location. It may be generalized or restricted, especially to the lower limbs. Sometimes eye movements show the same defect and the patient is unable to conjugately deviate the eyes quickly. The symptoms are worse during emotional stress and exposure to cold and there is one type in which the symptoms are present only on exposure to cold.

**Pathological Anatomy**—In this condition there are no objective signs in the nervous system. The muscle fibers are large there are many nuclei and the cross striations are poorly defined.

**Prognosis**—The disease is incurable but sometimes shows temporary arrest.

**Treatment**—It has been shown that quinine hydrochloride by mouth in doses of 2½ to 15 grains two or three times a day will consistently eliminate myotonus as a disturbing symptom\*. In this connection the section on myasthenia gravis (page 114) should be read.

### Myotonia Atrophica

**Synonym**—Myotonic dystrophy

**Definition**—A rare disease manifested by myotonia atrophy of special muscle groups and a family history of cataracts. The disease is familial and hereditary but some cases occur without such a history.

**Symptoms**—Myotonia is most marked in the hands and exhibits the characteristics described under Myotonia Congenita. The atrophy picks out cer

**Symptoms**—These may be apparent from birth or escape notice until it is found that the child cannot hold up its head and is incapable of maintaining other postures. There is an extreme hypotonia which prevents the child from sitting or standing or keeping its limbs or head in an unsupported position. The various parts can be moved voluntarily if they are supported. Because of the hypotonia the patient can be placed in unusual positions, the thighs can be flexed right up against the body wall so that the feet can be crossed behind the head. When the child is raised from the floor or bed by support in the axillae it tends to fall through these points of support, so that the shoulders are raised high and the trunk and head seem to be slipping through. Although the muscles are small, there is no localized atrophy, and there are no fibrillary twitchings in the muscles. Smooth muscle is not involved and the intercostal muscles and diaphragm escape. The tendon jerks are diminished or absent, faradic excitability is diminished or lost, and galvanic excitability is retained.

**Pathological Anatomy**—The muscles show the presence of some abnormally small fibers and some hypertrophied ones. In addition some apparently normal fibers remain. There is an increase in the number of nuclei in the muscles and an increase also in connective tissue. Changes in the anterior horn cells are discussed under the heading of Werdnig Hoffman Disease.

**Prognosis**—This disease tends toward gradual improvement, until the patient becomes able to walk and live actively.

**Treatment**—There is no specific treatment. Physiotherapy and training help while improvement is taking place.

### Werdnig Hoffman Disease

**Definition**—A disease clinically like amyotonia congenita but beginning later and having a familial history.

**Symptoms**—By many authors this is considered to be a type of amyotonia congenita. It occurs in siblings and there is also frequently a history of the same disease in previous generations or in collaterals. Before the onset of symptoms the child is apparently normal. At the age of two or three years the disease first manifests itself. The same type of weakness occurs but it is associated with atrophy and begins in the proximal parts of the limbs and then extends downward. There are no fibrillary twitchings and the same changes occur in the reflexes and electrical responses as in amyotonia congenita.

**Pathological Anatomy**—Grünir has described the following changes in the anterior horns of the cord in these two diseases. In amyotonia congenita he found a paucity of anterior horn cells and the presence of abnormal cell types without signs of degeneration. In the Werdnig Hoffman type of muscular atrophy there were signs of degeneration in the anterior horns with chromatolysis and vacuolization of nerve cells, neuronophagia, glial proliferation and signs of degeneration in the anterior nerve roots.

**Prognosis**—There is gradual progression and death follows within a few years.

**Treatment**—There is none known.

**Types**—(1) The pseudohypertrophic type of Duchenne In this type pseudohypertrophy of the calf muscles is a prominent feature and sometimes pseudohypertrophy occurs in the deltoid and other shoulder muscles as well. The chief difficulty is in the legs the gait is waddling, the children fall easily and they have difficulty in climbing stairs. They have the characteristic way of rising from a lying to a standing position described above. The large calves feel hard and unnatural, and late in the disease the hypertrophied muscles may also atrophy. This type is most common in childhood and in several members of a family and there is often no history of the disability in preceding generations. (2) Juvenile form of progressive muscular dystrophy or Erb's type In this type the shoulder girdle is first involved and then the condition spreads to the trunk, arms and thighs. The face, forearm and legs are involved only very late. (3) Facio scapulo humeral or Landouzy Dejerine type In this the muscles of the face, shoulder girdles and upper arms are affected and there is no hypertrophy. There may be difficulty in closing the eyes and wrinkling the forehead. The lips taper outward and the lower lip curves downward. When smiling, the corners of the mouth do not turn upward and the smile is 'transverse'. The infraclavicular region is flat and hollowed across the chest and the arms cannot be raised because of involvement of the deltoid muscles. Later muscles of the trunk may be affected and lumbar lordosis and an awkward gait appear. (4) Mixed types The types above described run true to form in a great many families and individual cases. Sometimes, however the distribution of the myopathy may be different and mixed types occur.

**Pathological Anatomy**—The pathological changes are in the muscles and not in the nervous system. Nevertheless these conditions are usually described in sections on neurology because of their similarity to neurological diseases and because a gradual transition occurs between the neurological and nonneurological types of muscular atrophy and weakness. Differentiation between the two is sometimes difficult. In the primary myopathies the hypertrophied muscles are made up of large swollen fibers with an increased number of nuclei, a loss of striations and some increase in connective tissue and deposition of fat. In the atrophied muscles and the hypertrophied muscles when they begin to atrophy the fibers are small, the nuclei diminished and the connective tissue increased. These two types of changes may go on side by side. Evidence of disturbance of muscle metabolism is found in an increased excretion of creatin in the urine.

**Prognosis**—The prognosis is bad as the atrophy and weakness progress.

**Treatment**—Treatment has been investigated along three lines (1) on the basis that endocrine dysfunction occurs (2) the use of adrenalin and pilocarpine on the assumption that there is a functional disorder of the autonomic nervous system (3) the use of glycine or other amino acids, in an effort to overcome the disturbance in muscle metabolism. Of these the last seems to be the only method that offers promise. Glycine in daily doses of 5 to 20 gm. at first increases the creatin output and then diminishes it and brings it to a normal level. Clinical improvement has been described at the same time.

tain muscle groups, the orbicularis oculi and oris, the sternomastoids, the muscles of the forearm and of the thighs. The atrophy may be extreme, especially in the sternomastoid muscles. Changes occur in the teeth and skin and hair. There is loss of tendon jerks, and sensory changes may occur. There may be excessive lacrimation and salivation. Cataracts occur characteristically in this disease, and often the evidence of heredity may be limited to the presence of cataracts, occurring at a young age, in the forebears of the patient. The disease begins usually about the age of twenty or thirty years but may begin at a younger age, especially in families in which it is well established.

**Pathological Anatomy**—There is a degeneration of muscle fibers and a proliferation of connective tissue. Reduction in the number of anterior horn cells has also been described.

**Treatment**—As for myotonia congenita.

### Hereditary Progressive Muscular Dystrophies

**Synonyms**—Primary myopathies, muscular dystrophy, myopathic atrophy.

**Definition**—A chronic, progressive disease manifested by atrophy and weakness of certain muscle groups, sometimes associated with pseudohypertrophy, and frequently occurring as an hereditary or congenital disease.

**Etiology**—Other than heredity there is no known cause. The disease is one of the muscles and apparently not of the nervous system.

**Symptoms**—The myopathies usually become apparent in childhood, sometimes a little later. In one family several members may show the condition and sometimes also it is to be found in preceding generations. The characteristic finding is atrophy in certain groups of muscles, and the myopathies have been subdivided depending upon the distribution of the atrophy. The atrophy is associated with weakness and both are progressive. Sometimes certain groups of muscles show hypertrophy or pseudohypertrophy. They become larger than normal but yet are not normal and are weaker than normal. Later in the disease these pseudohypertrophic muscles also atrophy. Males are more often affected than females and in one family the children of one sex may be involved and not those of the other. With the weakness there is clumsiness and these patients find great difficulty in using the involved members. The standing posture is characterized by a protuberant "pot belly" with markedly increased lumbar lordosis and with winged scapulae. The gait is waddling and awkward and difficulty is experienced in rising from a lying to a standing position. To do so the patient must roll over into a prone position with the face downward, raise the trunk on the arms and knees and then climb up on himself by pushing his body upward by means of his hands, placed at increasingly higher points on his legs. When he rises to a standing position he must then straighten up the trunk in the same way. With one hand on his knee he pushes himself upright, the other hand placed on the mid thigh continues the process and finally the upright position is attained. The reaction of degeneration (loss of faradic response and changes in galvanic response) is not usually found in these muscles.

**Pathological Anatomy**—Atrophic changes in the anterior horn cells and posterior columns occur. There is an hypertrophy of the interstitial tissues of the peripheral nerves and an atrophy of muscles and increase in fibrous connective tissue in them.

**Treatment**—None other than symptomatic.

### Hereditary Primary Optic Atrophy

**Synonym**—*Leber's disease*

**Definition**—Slowly progressive primary optic atrophy and blindness, occurring as an hereditary disease and beginning about the age of puberty. The condition is rare.

### Infections of the Nervous System

It is frequently difficult to define whether a disease of the nervous system is degenerative or inflammatory or toxic in nature. Inflammatory and degenerative changes exist side by side and frequently the etiological agent cannot be determined. The differentiation becomes even more difficult when one attempts to separate the inflammatory disease into those of infectious origin and those which are not infectious.

### Syphilis of the Nervous System

**Incidence**—It has been stated that some manifestations of syphilis are found in 10 per cent of autopsies and that 15 per cent of all nervous diseases are syphilitic in origin (Grinker). In cases of syphilis of the nervous system it is often impossible to obtain a history of primary infection as primary and secondary manifestations may be absent or escape notice. It seems in fact that the occurrence of secondary skin lesions diminishes the incidence of involvement of the nervous system and, conversely, that the absence of skin lesions increases the likelihood of cerebrospinal syphilis. The disease is more common in males than in females and it is possible that alcohol and trauma may predispose to its occurrence. The possibility of trauma as a predisposing factor by diminishing local resistance is of medico legal importance but must not be accepted too readily. Moore estimates that early involvement of the nervous system will occur about three times more often after inadequate or irregular treatment in the early stages than after no treatment at all. On the other hand the incidence of late nervous complications is not increased by inadequate or irregular treatment. Both early and late involvement of the nervous system is diminished by adequate treatment.

In about one half of the cases the nervous system becomes affected within three years of the primary infection. *Tabs dorsalis* and *general paresis* however develop later and frequently an interval of twenty to twenty five years may exist between the contraction of the disease and these complications. The fact that the disease may spread to the nervous system within such a short time and that it may manifest no symptoms or signs other than changes in the cerebrospinal fluid is an indication of the importance of routinely doing lumbar puncture on patients under treatment. During the first two years of

### Peroneal Muscular Atrophy

**Synonyms**—Charcot Marie Tooth atrophy, progressive neural muscular atrophy

**Definition**—An hereditary type of muscular atrophy involving the distal segments of the limbs and associated with pathological changes in the spinal cord and nerve roots

**Etiology**—The disease is usually hereditary and familial, but sporadic cases occur. No other etiological factors are known

**Symptoms**—The onset is usually about the age of puberty or before twenty years. The course is slow and progressive. The disability usually begins in the small muscles of the feet with atrophy and weakness. Somewhat later the same manifestations appear in the hands. The involvement of the muscles extends upward but the characteristic feature of the disease is that the spread is never beyond the elbows nor the lower third of the thighs. The atrophy and weakness are restricted to these distal portions of the limbs. Because of the involvement of the small muscles of the feet talipes develops and a pes cavus or equino varus deformity results. Fibrillary movements and coarse tremors may occur and the tendon jerks are diminished or absent. Electrical excitability of the muscles is usually altered with a diminution in the response to both faradic and galvanic stimulation. Paraesthesia and sensory impairment may occur. The appearance of the limbs is characteristic: the fully developed proximal segments and the atrophied distal segments resemble an inverted, long necked bottle. The symptoms occur symmetrically on the two sides. In the siblings of a patient instead of the typical signs being present, the only evidence of familial nature may be deformity of the feet.

**Pathological Anatomy**—There are degenerative and atrophic changes in the anterior and posterior nerve roots in the cells of the anterior horn and Clarke's columns in the cord and also in the posterior columns of the cord. The muscles themselves are atrophied.

**Prognosis**—The course is slowly progressive. Improvement is rare but the progress may be arrested.

**Treatment**—The only treatment is symptomatic physiotherapy for the wasting and weakness and special boots for the deformity of the feet.

### Hypertrophic Interstitial Neuritis

**Synonym**—Dejerine Sottas disease

**Definition**—A rare disease associated with thickened palpable nerves

**Etiology**—Other than that it occurs as an hereditary disease the etiology is unknown

**Symptoms**—In this disease also atrophy begins in the distal parts of the limbs and ascends. Pains sensory loss and incoordination also occur. Deformities of the feet and curvature of the vertebral column may appear. Occasionally Argyll Robertson pupils, nystagmus and cranial nerve involvement are also present. The superficial nerves are hypertrophied and palpable but not tender.

in which colloidal gold solutions are reduced by the higher concentrations of spinal fluid and not by the lower ones, the test cannot be used to differentiate the various types of neurosyphilis and may be positive in nonluetetic conditions. In general paresis and also in many cases of multiple sclerosis, the formula will be something like 5543200000 where 5 represents complete reduction. Other types of curve are 0001223200 or 0000012234.

### Meningovascular Syphilis

**Definition**—In this type of neurosyphilis the chief involvement is of the mesodermal tissues, the meninges and blood vessels. A further subdivision may be made into meningeal vascular and meningovascular types.

**Symptoms**—The involvement may be primarily meningeal or primarily vascular or both. Syphilitic meningitis may be acute or chronic and may occur at any time during the disease. In most cases symptoms develop within three or five years of the original infection. The acute and chronic types are essentially the same in character but vary in severity. In the acute type all the signs of meningitis may be present. The neck is stiff and painful on movement and there is a positive Kernig sign. Headache is a prominent symptom and is usually worse at night. Fever, nausea, vomiting, clouding of consciousness and delirium occur. In chronic meningitis also headache is frequent, is often worse at night and may be associated with tenderness on pressure of the skull. Fever is less common but sometimes occurs and nausea and vomiting may be present. Mental symptoms are frequent, they are more fulminating in acute meningitis and progressive in the chronic form. Apathy, confusion, impairment of memory, and stupor are common. These types of meningitis are usually basal although the infection may spread up over the vertex. The most characteristic focal signs are those of cranial nerve paralyses and the third nerves are particularly often involved. Anosmia, optic neuritis, scotomata, defects in visual fields, papill edema and secondary optic atrophy, paralyses of ocular movements, ptosis, loss of the pupillary reflex to light, paralysis of the muscles of mastication or of the face, tongue or palate, and nerve deafness may all occur, depending upon the nerves involved. Convulsions, either focal or general, may be present and are sometimes followed by residual paralysis.

The cerebrospinal fluid in these cases is under increased pressure, the globulin and total protein are increased. The cell count is increased according to the acuteness of the process and may number from 10 to 20 lymphocytes to thousands per cubic millimeter. The spinal fluid Wassermann is frequently negative in this condition and the differentiation from tuberculous meningitis may be difficult in the acute form.

The vascular type of neurosyphilis is due to endarteritis of smaller or larger vessels. The process may be a diffuse change which will gradually lead to occlusion of small vessels without prominent focal symptoms or the occlusion of a large branch, most often of the middle cerebral artery, with prominent focal symptoms. These changes may occur at any time during the course of the syphilis and must be carefully excluded in cases of hemiplegia in young people below the age of forty or forty five years. Indications of the diffuse involvement are headache, irritability, mental changes and sometimes con-

treatment the cerebrospinal fluid should be examined at least at six or eight month intervals. Determination of the blood Wassermann reaction is not enough, as this may be negative while the cerebrospinal fluid Wassermann is positive. There is much clinical evidence to support the belief that there is a neurotropic type of treponema which is particularly likely to involve the nervous system. The high incidence of cerebrospinal syphilis in husbands and wives, and in patients infected from one source, is an indication of this. It is important therefore that the families of patients with this disease be examined as well as the patients themselves.

**Types**—Cerebrospinal syphilis has been divided into different types determined by the clinical and pathological findings. In this section the following divisions will be made: asymptomatic neurosyphilis, meningovascular syphilis, tabes dorsalis, general paresis, gumma, congenital syphilis. It must be borne in mind that cerebrospinal syphilis can manifest itself by any group of symptoms and is not confined to the above clinical types. The most common findings in all these clinical cases are the changes in the cerebrospinal fluid and of these the positive Wassermann reaction is the most typical. This reaction is not positive in all cases, indeed in many it is negative. In as many as 30 per cent of cases with positive spinal fluid Wassermann reactions, the blood will be negative so that examination of the latter alone is not sufficient. When these reactions are negative, it is sometimes possible to render them positive by the administration of a provocative dose of an arsenical preparation. Novarsenobenzol 0.3 or 0.4 gm, in 10-15 cc of sterile distilled water, may be given intravenously and the tests repeated in about five days.

### Asymptomatic Neurosyphilis

**Definition**—Evidence of involvement of the nervous system shown by changes in the cerebrospinal fluid without clinical signs or symptoms.

Changes in the cerebrospinal fluid may occur at any time during the course of syphilis. These may be increase in pressure, slight increase in cells, increase in globulin, a positive Wassermann reaction and reduction of colloidal gold (positive Lange reaction). All or any of these may be present without abnormal signs being apparent on physical examination. The normal cell count in the cerebrospinal fluid is from 0 to 10 lymphocytes per cubic millimeter and this number is often slightly increased in asymptomatic neurosyphilis. Various tests exist to show the presence of excess globulin and the simplest of these is the Pandy reaction. This is done by dropping cerebrospinal fluid into a test tube containing 1 per cent phenol solution. As the drops descend in the phenol solution, they will turn milky white when globulin is in excess. This test is a very sensitive one. The reduction of colloidal gold in solution is a reaction depending upon the ratio of albumin and globulin present. In carrying out the test colloidal gold solution is added to spinal fluid diluted with saline to different concentrations and arranged in a row of test tubes with the higher concentrations to the left. Precipitation will take place in some tubes and not in others and the degree of this will vary so that a curve can be plotted. Apart from the fact that a typical curve exists in general paresis



endothelial cells, and the elastic layer splits. The vessel becomes occluded and is surrounded by an area of softening. The meningitis is usually a diffuse leptomeningitis with infiltration with lymphocytes. This may involve the spinal as well as the cerebral meninges. The dura may become involved and thickened. In late cases there is connective tissue proliferation and the pia arachnoid becomes thickened. The meningitis is most marked at the base of the brain and spreads upward into the Sylvian fissures. Small gummata are frequently present in the leptomeninges and about the blood vessels. These are granulomata made up of a dense accumulation of fibroblasts, lymphocytes and plasma cells. New blood vessels form in them and the center breaks down, becomes necrotic and filled with fibrous tissue. The inflammatory process in the meninges and the occlusion of blood vessels cause softening and degeneration within the nervous parenchyma.

### General Paresis

**Synonyms**—General paralysis of the insane, dementia paralytica.

**Definition**—The most serious type of neurosyphilis, caused by direct extension of spirochetes to the nervous parenchyma and manifested by mental and physical signs.

**Symptoms**—This is a late complication of syphilis which usually develops from ten to twenty years after the original infection. The symptoms can be divided into mental and physical groups. Males are affected about four times as often as females.

**Mental Symptoms**—These may begin insidiously and progress for some years before their full significance is appreciated, or they may be marked from the onset. They may be described under the headings of intellectual changes, delusions and affective disorders, although these designations do not define different types of general paresis. The first indication of impairment of mental ability is usually difficulty in carrying on business matters or work as efficiently as before. This may be attributed to the age of the patient or to some other factor and its gravity may be missed. The intellectual change is a gradual deterioration which may progress to dementia. The patient becomes careless and inefficient about his work, he is less trustworthy and becomes forgetful, inattentive and unable to concentrate. He has a poor comprehension of details and loses his ability to deal completely with matters of ordinary routine. His judgment becomes impaired so that he is likely to lose money or to undertake contracts which he is unable to fulfill. He commits himself cheerfully to the expenditure of sums far beyond his means and because of this may become involved in legal suits. He grows careless about his habits and personal appearance, will neglect to wash or shave or wear clean clothing. Sometimes he may develop Korsakoff's syndrome with fabrication to make up for his deficient memory of recent events. Finally he may become disoriented, demented, bedridden and completely unable to look after himself. Sometimes sexual excesses and perversions are present and may require restraint of the patient.

As these intellectual changes are progressing, delusions may appear. Those described as typical of the condition, although they do not by any means

**vulsions** When larger vessels are involved, focal symptoms appear such as hemiplegia, bulbar paralysis and pseudobulbar paralysis. Of these by far the most common is hemiplegia which may take a few days to develop and is likely to show considerable improvement. It is due to involvement of the pyramidal tract, usually in the internal capsule, and shows the signs discussed on page 987. Occlusion of branches of vessels to the medulla may cause softening there and paralysis of cranial nerve nuclei. The resultant symptoms are dysarthria, dysphagia and dysphonia, from weakness of tongue, palate, pharynx, lips and vocal cords. The speech becomes unintelligible, because of the defect in articulation and not in higher speech functions. Swallowing is difficult and fluids regurgitate through the nose. In severe cases the patient may be unable to clear the mouth, throat and trachea of mucus and saliva, the mouth hangs open and the tongue is heavily coated. Pseudobulbar paralysis is due to paralysis of the upper motor neurone components of these cranial nerves and produces dysarthria, usually bilateral pyramidal tract signs and emotional instability. In these cases of vascular syphilis both the blood and spinal fluid Wassermann reactions may be negative. The globulin in the fluid may be slightly increased and there may also be a slight increase in the number of lymphocytes.

The most characteristic single physical finding in cerebrospinal syphilis is the Argyll Robertson pupil. This has already been discussed on page 1002. The typical Argyll Robertson pupils are contracted, unequal on the two sides, irregular, and inactive to light but active on accommodation. All these changes are not present in all cases and the pupils may be equal and regular but inactive to light or irregular and unequal and sluggish to light. It has already been mentioned that tonic pupils which react very slowly, so slowly that the reaction may be missed, do not indicate syphilis, but these are rare. As they may be associated with loss of knee jerks the resemblance to syphilis is all the closer (Adie's syndrome). In the presence of any of the abnormalities described above, syphilis is the first cause to be considered and the patient must be very carefully investigated.

Meningovascular syphilis may also affect the spinal cord and cause softening, by vascular occlusion and extension of the inflammatory process. The condition is then called myelitis or meningomyelitis. It usually occurs in the thoracic region and causes a spastic paraplegia (upper motor neurone paralysis of the legs) and sensory impairments up to the level of the lesion. Root or girdle pains are common because of involvement of the posterior nerve roots by the meningeal inflammation. Retention of urine followed by incontinence frequently occurs. The cord lesion may be severe enough to cause the signs of transection of the cord with a flaccid paraplegia being followed by increase in tonicity and flexor spasms of the legs. On the other hand the only physical signs may be those of bilateral pyramidal tract involvement. The changes in the cerebrospinal fluid are the same as those described above with some times in addition the signs of subarachnoid block on manometric tests.

**Pathological Anatomy**—The changes in the blood vessels are primarily those of an endarteritis. The adventitia and media are infiltrated with lymphocytes and plasma cells; there is proliferation of the intima and sometimes of the

tricles are larger than normal and the subarachnoid space is widened. The convolutions are atrophied and small and the sulci are widened these changes are usually more marked in the frontal lobes. The ganglion cells show different stages of degeneration and some disappear so that the cyto architectonics are altered. The pia arachnoid is opaque and thickened and infiltrated with lymphocytes and plasma cells. The dura may also be thickened and adherent and show evidence of a hemorrhagic pachymeningitis. There is ependymitis of the ventricular walls which become granular in appearance. The perivascular spaces become densely infiltrated with lymphocytes and plasma cells. There are patchy areas of demyelination, and degeneration may also descend into the



Fig. 404.—Spirochetes in the brain of a patient with general paresis. (From Grinker, Neurology, Courtesy of Charles C. Thomas, Publisher, Springfield, Ill.)

spinal cord. Fibrous glia proliferate to form a dense meshwork in the cortex and along the infiltrated vessels and ameboid glia are present. The microglia also increase and form rod cells which are characteristic of this condition. In about half the cases spirochetes can be demonstrated in the cortex and sometimes in the ganglion cells (Fig. 404). Very characteristic of paresis is the presence of iron in the perivascular spaces, adventitial tissue, microglia and free in the brain. The signs of meningo-vascular syphilis may also be present in general paresis.

**Prognosis**—The prognosis of general paresis has been greatly altered by the newer forms of treatment especially fever therapy. Untreated cases die

occur in all cases, are delusions of grandeur. The patient believes himself to have unlimited power and wealth, he regards himself as the author or engineer of tremendous projects and he busies himself by acting in accordance with these delusions. Frequently he will buy large numbers of things for which he has no need, and cannot pay and will distribute largesse to all with whom he comes in contact. He becomes a nuisance to those in charge of him and to unsuspecting shopkeepers who are the recipients of his orders. All this is carried out with a show of tremendous energy and with a cheerful expansiveness. These patients are often euphoric and have an unjustified sense of strength and of well being. Even when quite ill they will state that they never felt better and that they are doing wonderfully well. Delusions of the infidelity of a marital partner are also common. Hallucinations are not common in this disease.

Affective disorders, or disturbances of mood, occur commonly. The patient may be depressed, worried, anxious or agitated, or, on the other hand, excited and maniacal. At the beginning of general paresis there may be good insight on the part of the patient, but this disappears in more marked cases so that they have no appreciation of their conduct as abnormal.

**Physical Signs**—These may be present before mental changes become apparent or they may be absent even in the presence of mental changes. They may vary considerably and may consist of signs of *tabes dorsalis* as well as of general paresis and the condition is then called *taboparesis*. The facies is often vacant and smoothed out and there is frequently a silly smile or grin upon it. Argyll Robertson pupils or some of the features of them usually occur. The speech is slow and slurred and some syllables are left out or run together. Tremor of the face, lips, tongue and fingers is usually present and may interfere with such movements as those of writing, which becomes shaky and uneven. In addition letters or syllables may be left out of written words just as they sometimes are out of speech. Impairment of power may develop and sometimes apoplectic attacks with hemiplegia, and the usual signs of upper motor neurone lesions occur. The tendon jerks are usually increased, but, if some tabetic manifestations are present as well the knee and ankle jerks are absent. The plantar response will be extension if hemiplegia has occurred and sometimes also without gross disturbance of power. Epileptic attacks, either focal or general, are not uncommon. Ataxia with impairment of gait, optic atrophy and incoordination of arm movements may be evidence of a combination of *tabes* and *paresis*. Loss of sphincter control and uncleanness are evidences of the mental rather than the physical conditions.

The cerebrospinal fluid is under slightly increased pressure and the lymphocytes are increased but not usually beyond 100 per cubic millimeter. The total protein and globulin are both increased and colloidal gold solutions are reduced in the first zone and reported as 555-4321000 or a similar formula. This same type of Lange curve occurs in about half the cases of multiple sclerosis. The cerebrospinal fluid Wassermann is positive and the blood Wassermann almost always the same.

**Pathological Anatomy**—In general paresis pathological changes in the brain are widespread. The brain is atrophied and shrunken so that the ven-

rived. In addition to the changes in position and vibration sensibility there are also abnormalities of pain sensibility. Deep pressure pain is frequently lost so that squeezing muscles, or the tendo Achillis or the testicles, will not evoke pain. In some cases fractures of the leg have been sustained, impacted and gone unnoticed until accidentally discovered on examination. Superficial pain sensibility also becomes impaired in certain characteristic areas. These run over the bridge of the nose on to the cheeks in the shape of a butterfly across the chest from the level of the second rib to the costal margin, on the inside of the arms and forearms, on the outer border of the legs below the knee, on the feet and in the perianal region. In these locations apart from diminution in pain sensibility there may be a marked delay in its appreciation so that if the skin is pricked with a pin several seconds elapse before the pain is felt by the patient. Other forms of superficial sensibility may or may not be impaired later.

Normal equilibrium at rest and on movement is a function which requires both sensory and motor integrity. To carry out voluntary movements properly, we must be able to will them, to move the parts to coordinate the movements and also, through position sensibility to know at each moment whether the desired movement is being carried out and also at what stage of its execution it is. Sense of position consequently must guide us at all times and must be there to inform us that the movement we wish to do is being done. Without this guide we can still carry out movements fairly well if we watch the parts involved and see that they are doing their jobs properly but this method is not as quick nor as efficient as muscle and joint sense. With loss of sense of position therefore there is impairment in motor function and this type of impairment is ataxia.

The first evidence of this ataxia is usually an unsteadiness in walking and turning and this is worse when the eyes are closed. As it progresses the patient attempts to compensate for it by walking with the feet widely separated by raising the feet higher from the ground than normal and by bringing them down violently on the surface that is being walked upon. The disability is worse in the dark when vision cannot be used as an aid and the patient will sway and stumble and perhaps fall. Gradually one stick will have to be used then two and finally walking becomes impossible. While this locomotor ataxia is developing there are also other evidences of ataxia. If the patient is told to touch the nose with the finger he will be able to do so with his eyes open but not when they are closed and he must be guided by sense of position alone. The same difficulty is experienced in placing one heel on the opposite knee. If he is told to stand with the feet together and the eyes closed he will sway unsteadily (Romberg's sign) and the same thing will be noted as he stands before a wash basin and covers his face with his hands as he washes. Voluntary movements consequently become much impaired but in addition, involuntary irregular jerky movements may occur of which the patient is not aware unless he sees them. If he is asked to hold the arms outstretched and still it will be found that if he closes his eyes the arms and fingers will move irregularly.

within two or three years. With malaria treatment it is possible to obtain remissions in 30 to 40 per cent of cases whereas spontaneous remissions occur in only 10 to 20 per cent.

### **Tabes Dorsalis**

#### **Synonym —Locomotor ataxia**

**Incidence**—This occurs more often in males and, as in other forms of cerebrospinal syphilis, there may be no history of primary or secondary manifestations of the disease. It usually occurs years after the initial infection just as does general paresis.

**Symptoms**—While certain definite symptoms are characteristic of this disease, many atypical symptoms may be present in an individual case. As the disease involves principally the posterior nerve roots and their fibers which ascend in the posterior columns, sensory disturbances are a prominent feature of the symptomatology.

Pain may be the first symptom of which the patient complains and its significance may be missed for a long time during which it is vaguely labelled "rheumatism". At first the pain may be dull and aching but eventually it assumes the character of "lightning pains". These are severe, knifelike pains, which are felt chiefly in the legs but may occur in the arms or face. They may occur daily or in attacks lasting for some days or weeks and then followed by a period of relief. They are worse at night and in cold, damp weather, and they are also aggravated by constipation and intercurrent illness. The patient describes them as if a knife or a hot bat were shoved into his skin at right angles and deep into the flesh. The pains may remain at the same spot for a time or may jump about and they sometimes leave the skin reddened or ecchymotic. Each pain lasts but a few seconds but they occur in paroxysms. Girdle pains and root pains also occur and are severe. They follow the distribution of posterior nerve roots either around the body like a belt or down the limbs. They occur also in attacks, but in the interval there may be a constant feeling of tightness in the same segmental distribution. Paraesthesias occur and the common ones are a feeling of cold and numbness or the feeling that one is walking on wool or a carpet. These paraesthesias frequently occur across the chest and on the inside of the hands and forearms. In addition the patient may be aware of diminished sensibility of his skin may be hypersensitive to tactile and thermal stimuli. These sensory disturbances are probably due to irritation of the posterior roots by inflammatory reactions in the meninges.

Sensory losses are most marked for those types of sensibility which traverse the posterior columns. This impairment usually occurs in the legs but may begin in the arms in cases of so called cervical tabes. Vibration sensibility, position sense and sense of passive movement are impaired. The vibrations of a tuning fork placed upon a bony point will not be felt and passive movements of the toes or other segments of the limbs cannot be appreciated unless seen. Because of this loss of position sensibility the patient is ataxic and it is from this symptom that the name locomotor ataxia is de-

swollen, and there is an increase of synovial fluid. The articular surfaces erode and atrophy and at the same time proliferative changes occur and loose bodies appear in the joint. The result is swelling, subluxation, and marked deformity. The knee joint is most often involved, but the condition may occur in other joints as well. It is usually painless. The same type of arthropathy may occur in syringomyelia.



Fig. 405.—A Charcot knee joint in a case of tabes dorsalis.

Mental symptoms may occur in tabes and frequently a combination of tabes and paresis exists and is known as taboparesis. In addition signs of meningo-vascular syphilis may be present though this is uncommon.

The foregoing signs and symptoms are those of typical fully manifested tabes dorsalis. As in all other diseases atypical forms exist and all the symp

It was stated earlier in this chapter that the preservation of tone depends upon the integrity of the reflex arc. It was noted that lower motor neurone lesions by breaking the efferent pathway of that arc diminished or abolished tone. In tabes dorsalis the afferent pathway of the arc is broken and again tone is diminished or abolished. Because of this, hypermotility of the joints is possible, the hip can be fully flexed on the abdomen and the knee can be hyperextended. In many old tabetics the legs are bowed, with the concavity forward, because of this hyperextension of the knee, and when tonicity is tested, the surfaces of the knee joint can be actually felt to bounce against one another and to rebound. Again because of a break in the afferent pathway of the reflex arc the tendon jerks are at first diminished and then lost. As tabetic signs are usually more marked in the legs, the tendon jerks may be abolished only in them and not in the arms. In the process of becoming diminished, they may be unequal on the two sides. The superficial reflexes are not altered.

The Argyll Robertson pupil is characteristic of tabes and occurs almost always in this form of neurosyphilis. Primary optic atrophy occurs frequently and may become complete so that blindness supervenes. It has frequently been noted that when optic atrophy develops ataxia in the extremities does not occur or does not become marked. Paralysis of external ocular movements of the sense of smell and of hearing sometimes occurs.

Disturbances of bladder function are common. At first this is usually retention so that the patient may go for many hours without voiding. It is found on cystoscopic examination that the bladder is relaxed and thin and that the posterior urethra is insensitive. Later dribbling begins to occur and finally there is complete incontinence. Sexual impotence also occurs frequently.

Crises are a particularly disagreeable symptom of tabes. They are pains referred to an organ of the body, usually the stomach. They may occur periodically or at irregular intervals, and they begin and end suddenly. Gastric crises consist of intense sharp abdominal pain which may be continuous or intermittent. The patients cannot eat or drink and if they do they vomit. Even without eating or drinking there is constant retching and the regurgitation of bile stained gastric contents. Such an attack may last for hours or days. Rectal crises consist of pain in the rectum, a constant desire to defecate without results and tenesmus. Bladder crises consist of pain in the bladder and a constant desire to micturate. Laryngeal crises consist of pain in the larynx, cough, dyspnea and stridor. Many laparotomies have been carried out because of mistaken diagnoses in cases of gastric crises.

Trophic disturbances may be present in tabes because of the disturbances in pain sensibility. Perforating ulcers of the feet occur on the sole on the ball of the big toe. They may begin as a callus which breaks down to form an indolent chronic ulcer. This is small and circular and may extend deeply enough to involve the bone in an osteomyelitis. Fractures may occur without pain and heal slowly with an excess of callus formation. Bed sores are particularly likely to occur in bedridden incontinent patients. A particular type of arthropathy known as Charcot joint (Fig. 405) is a not uncommon complication. This may follow a slight trauma. The joint becomes



convulsions are usual, and there is frequently some hydrocephalus although this does not lead to deformity of the head like infantile hydrocephalus. Pupillary abnormalities such as the Argyll Robertson pupil, optic atrophy, cranial nerve involvement, hemiplegia and diplegia and disturbances of growth and nutrition are common. The parietic form may first manifest itself between the ages of ten and fifteen years, and it follows a slow course. Tabes dorsalis may not be evident until early adult life. The blood Wassermann is almost always positive, and the cerebrospinal fluid shows the same changes as in acquired syphilis. The prognosis is poor.

### Treatment of Neurosyphilis

The treatment of neurosyphilis is an individual problem and has to be varied to meet the requirements of the particular case. It is carried out in courses depending upon the type and severity of the syphilis and the general health and physique of the patient. The chief agents used are metallic preparations, penicillin and the induction of fever. The metallic preparations, their dosage, the mode of administration and the undesirable reactions which may follow the use of these preparations are discussed in Chapter XIX. The reactions which are of particular importance from the standpoint of neurology are the Hershheimer reaction and the ocular complications following the use of tryparsamide. The Hershheimer reaction follows the activation of the syphilitic focus and the liberation of toxins due to intensive treatment with arsenic or penicillin. It follows soon after the beginning of treatment and the signs will depend upon the situation of the activated focus and the structures involved by the toxins. They may be generalized or they may be focal such as the paralysis of a cranial nerve or hemiplegia. Tryparsamide frequently causes subjective blurring of vision and sometimes optic atrophy. This is a serious complication as blindness may ensue. The drug should consequently not be used in cases of optic neuritis nor of partial optic atrophy and during its use the fundi should be examined regularly. A special technique for the administration of arsenic is the Swift Ellis method. This is not used a great deal and any special benefit which it may have seems to apply to cases of developing optic atrophy and severe lancinating pains. The technique is complicated and need not be discussed here but the treatment consists in the administration of salvarsanized serum into the subarachnoid space in the lumbar or cisternal region.

The use of fever treatment in paresis and taboparesis is a decided therapeutic advance. It should be used as soon after the diagnosis is made as possible. The most efficacious means of inducing the fever is by the inoculation of malaria. The malarial blood of one patient is given to another and after a variable incubation period the second patient develops the malaria. The tertian type is ordinarily used and the injection of blood may be given intravenously or subcutaneously. The best time to take blood from the one patient is immediately before a paroxysm. If the administration to the second patient is to be intravenous 15 c.c. of blood are used while if it is to be subcutaneous about 10 c.c. are used. In the former case the blood may be citrated but in the latter case if the transfer is to be made immediately this

toms of the disease need not be present. The picture outlined above was common 30 years ago, but it is surprising how seldom a typical tabetic is encountered today. Most of the present day tabetics have few signs in addition to Argyll Robertson pupils, absent knee and ankle jerks, some ataxia, some pains and changes in the cerebrospinal fluid. Whether this is an indication of the efficacy of the treatment of the past fifteen years, whether it is due to attenuation of the treponema or whether it is due to changes in our mode of living, it is impossible to say.

**Pathological Anatomy**—The posterior nerve roots are smaller than normal and there is marked degeneration of the fibers ascending in the posterior columns. As fibers from the lower thoracic and lumbosacral regions are chiefly affected and as the fibers in the posterior columns are pushed medially as they ascend, the degeneration in the cervical region is chiefly in the column of Goll and less so in the column of Burdach. In the area of degeneration there is dense gliosis. The blood vessels are small and sclerotic and the pia arachnoid is thickened. In addition pathological changes have been described in other structures of the cord.

**Prognosis**—This varies considerably. The disease is not often rapidly progressive and many cases do not advance to a point of incapacity. The response to treatment is also variable and some patients show considerable improvement. In some the course is arrested, while in others there is a progressive advance in the symptoms.

### Gumma

Gumma of the brain is the rarest of the nervous manifestations of syphilis, and it is the rarest type of cerebral tumor (Grinker). Multiple small gummata occur in meningo-vascular syphilis, but large isolated gummata sufficient to cause symptoms of an intracranial tumor are very rare. When they do exist they arise from the meninges and grow into the brain. Their signs are those of an intracranial tumor with the general manifestations of increased intracranial pressure and focal signs depending upon their location. As they respond but slowly to antiluetic treatment operation may be necessary to save the eyesight of the person. They occur also in the spinal cord. A positive Wassermann reaction and signs of intracranial tumor are not sufficient to make a diagnosis of gumma of the brain, as both syphilis and tumor may coexist, and sometimes in tumor of the brain there is a weakly positive Wassermann reaction in the spinal fluid.

### Congenital Syphilis

Congenital syphilis and its treatment will be described in Chapter XIX. The nervous system is frequently involved and may show signs of a diffuse encephalitis, meningo-vascular syphilis, tabes dorsalis or general paresis. The diffuse encephalitis occurs early in life, is manifested by widespread acute signs, and terminates fatally; convulsions are common in this condition. The other types of congenital neurosyphilis are essentially like those in the acquired form. The most common is the meningo-vascular type. Mental deficiency and

## MENINGITIS

### Pachymeningitis

**Definition.**—An inflammation or infection of the dura mater

**Etiology.**—Pachymeningitis may occur in syphilis. It may be due to infection secondary to an osteitis of the skull or vertebral column, and it may follow head injury. It is frequently associated with the formation of an abscess and this pathological condition is described later.

### Pachymeningitis Interna Hemorrhagica

**Definition.**—This condition is really one of chronic subdural hematoma and will be discussed under that heading (see page 1102)

### Leptomeningitis

Before considering the specific types of leptomeningitis the general symptomatology of this condition will be described. The severity of the neurological symptoms will depend upon the acuteness of the pathological condition in the meninges and the general systemic symptoms will depend upon the type and acuteness of the infection which is responsible for the meningitis. The characteristic symptoms of acute meningitis are headache, stiffness of the neck, retraction of the head, positive Kernig and Brudzinski signs and the presence of the products of inflammation and frequently also the etiological agent in the cerebrospinal fluid. Such meningeal irritation may occur from infection, inflammation and the presence of foreign substance such as blood in the subarachnoid space. Kernig's sign is inability to extend the lower leg completely when the thigh is flexed at right angles or more on the abdomen. Brudzinski's sign is a flexion of one leg when passive flexion is made of the other or flexion of both legs when the neck is bent forward on the chest. In severe cases irritation may be sufficiently great to cause marked hyperextension of the entire body, a condition known as opisthotonos. In addition to these nonfocal signs of meningeal irritation there may be signs of focal involvement of the cranial nerves or of cortical centers in the brain. Consequently in acute leptomeningitis headache, photophobia, vomiting, fever, slow pulse, convulsions and signs of cortical irritation or depression are frequent.

### Specific Infections of the Meninges

The specific infections of the meninges may be caused by an invasion of bacteria or allied agents. These usually are conveyed to them either by the blood stream or by direct contamination through the lymphatics or contiguous destruction of tissues. The symptoms produced by these infections have been described above and the technic of lumbar puncture was described on page 1020. The specific infection may be identified by staining and bacteriological methods or shrewdly suspected by more indirect methods. There are few forms of meningitis that are in any manner specific infections as the majority are due to organisms which may be said to involve incidentally or indirectly these tissues as part of a general or local disease. The more specific will be dealt with first.

is not necessary. Immediately following the injection of blood there may be a rise in temperature for 24 to 48 hours unless the blood has been typed beforehand. The incubation period varies from three to twenty days or more and before the establishment of definite periodic chills there may be a continued, irregular fever for a few days. Advanced age, cardiovascular renal disease and malnutrition are contraindications to this treatment. The patient should have from 8 to 12 rises in temperature of 103° F or more. After the chills have begun, rectal temperatures should be taken every two hours and during the chills every half hour. If the systolic blood pressure falls below 80 mm of mercury or marked tachycardia is persistent, the treatment should be stopped. The malaria can be stopped by the administration of quinine 0.3 gm three times a day and this should be continued for about two weeks. After the treatment has been completed, the return of the patient to activity should be slow.

Fever may also be induced by the intravenous administration of typhoid paratyphoid vaccine. The initial dose of this is 50 million organisms in about one or more cubic centimeters of normal saline solution given slowly intravenously. Successive doses will have to be doubled each time or even more greatly increased. Better results may follow dividing the dose and giving the second fraction from one to three hours after the first. Fever can also be induced by physical means by the use of short wave electrical apparatus, but this requires special equipment. Of the various means of inducing fever malaria seems to have the best therapeutic effects so that the result must come not from the fever alone.

Potassium iodide seems to be particularly of value in productive lesions and in gummata. It is very soluble and can be dispensed in water and taken well diluted. It may be given in doses of 10 gm three times a day, gradually increasing to a total of 12 gm a day or more. In acute syphilitic meningitis much larger doses will be of value.

The treatment of neurosyphilis by chemotherapy and antibiotics follows the same lines as that of syphilis in general (Chapter XX). But here again this at present is in such a state of transition and flux that opinion as to the best method to be employed seems to change almost monthly. Although penicillin is now a favorite drug to use the best interests of the patient would be served by having a line of treatment outlined by a consultant or by referring the patient to a special clinic as in tuberculosis.

In *tabes dorsalis* apart from medicinal treatment, reeducation may be of great value in enabling the patient to compensate for his impaired position sensibility and so to improve the ataxia. We pay little conscious attention to our ordinary movements as sense of position takes care of their proper regulation and will inform us if they are not being properly carried out. The tabetic can learn to compensate for the impairment of his sense of position by relearning consciously how to carry on his ordinary movements. His walking, sitting down and getting up etc. will be greatly improved by relearning how to do them properly.

depends upon the relative balance of immunity and virulence. The symptoms may be present for a few hours or days and the infection progress no further, the true cause being unrecognized and the patient being a carrier (see p. 1070) or they may persist for days or weeks and the same result occur. On the other hand, within minutes or in other cases delayed to hours, days, weeks, and sometimes years, the infection may explode into a septicemic invasion.

In conformity with many specific infections such as typhoid fever, tuberculosis or syphilis, the protective barriers of the portal of entry may be overthrown and the infection become a *septicemia* or *bacteremia* with all the general features of severe systemic prostration, pyrexia, leucocytosis and splenomegaly. Here again the severity and duration of the symptoms are determined by the relative resistance of the host and the virulence of the invader. The bacteremia may last for a few hours or days or again for months with out involvement of the meninges. Recovery may take place promptly or after a period, or death may occur from the septicemia in a life order of time. It is usual, however, in the great majority of the septicemic cases for the meninges to be involved within forty-eight hours.

This development marks the third or *meningeal stage*. All the symptoms and signs of meningitis as outlined above appear in rapid succession—headache, apathy, irritability, rigidity of the neck, hypertonia, Kernig and Brudzinski signs, opisthotonos, convulsions, delirium and coma in their varying degrees of intensity. The recognition of the anatomical lesion is now not difficult. This stage may be called the localized or metastatic lesion of the bacteremia similar to the arthritis of the gonococcus or the skin rashes or mucous patches of syphilis. It is true that these three stages—nasopharyngitis, bacteremia and meningitis may not be clear cut and constant in their elapsed time and severity but they are in their sequence. It is the former variations which have led to the following clinical classification. It is given with some hesitance as it implies distinct types of disease rather than variations of sequential intensity.

- I *Regular type*—all phases relatively moderate—death or recovery six to fourteen days
- II *Bacteremic type*—general symptoms dominate the meningeal
- III *Meningeal type*—cerebro spinal symptoms dominate
- IV *Malignant or fulminant type*—death occurs in a few days—shortest reported five hours—most likely due to overwhelming septicemia even though meningeal signs may be present
- V *Relapsing type*—recurring exacerbations or relapses of the infection
- VI *Chronic type*—any of the above going on to a progressive productive meningeal lesion which produces signs of increased intracranial pressure, hydrocephalus or cranial nerve palsies

Before proceeding with the consideration of the last two types it would seem best to deal with certain symptoms and signs which are not directly due to the meningeal lesion. As one of its older synonyms—spotted fever—implies there are frequently skin manifestations. These consist of purpura, petechiae and a large macular lesion which varies from a yellow red to a pink red color. The former appear soon after the onset, and the last about the third or fourth day. They are significant of a systemic meningococcal infec-

### Epidemic Cerebrospinal Meningitis

**Synonyms**—Meningococcic meningitis, spotted fever

**Definition**—This is a form of leptomeningitis due to a specific infectious agent and is communicable, occurring both sporadically and in epidemics. It was first described as a clinical entity by Vieuxseux in 1805, and the causative agent, the meningococcus, was determined by Weichselbaum in 1887.

**Etiology**—The cause of epidemic meningitis is the meningococcus which is a gram negative biscuit shaped diplococcus. It is commonly intracellular and closely resembles the gonococcus in its morphologic, staining, cultural and biologic characteristics. It is a specific for the cerebrospinal system as the gonococcus is for the genitourinary. Both may be found in other sites of infection but these are exceptions rather than the rule. They both grow best on dextrose media which contains defibrinated blood and at a pH of 7.6 to 7.8. There are four immunologic types of the meningococcus. Group I conforms to the original strain of Weichselbaum while II is the parameningococcus of Dofter, and III is closely similar to I, and IV to II. The importance of appreciating the fact that there are these different types will be referred to under Treatment.

**Incidence**—Children are much more susceptible than are adults in whom, as a rule there is a high natural immunity. The infection is widespread through the world having been reported from practically all countries but chiefly in the north temperate zones. In large centers of population, particularly in North America there are constantly reported sporadic cases. On the other hand the severest epidemics have occurred in rural districts. The factors leading to epidemics are not known. There is a rough periodicity occurring about every ten to twelve years. For further details of its epidemiology, the reader is referred to works of Webber and Hirsch.

The disease is found throughout the year, but is most prevalent in the winter and spring months. This is accounted for by the closer contacts at these periods as the disease is conveyed by droplet infection and to the fact that this is the time of the year when the majority of such diseases spread in the population which may be more susceptible on account of the prolonged absence of the effective solar rays. No age is immune. Males are slightly more liable than females which ratio is made conspicuous through epidemics occurring in camps and barracks.

**Symptoms**—The incubation period is commonly held to be from three to five days and the portal of entry is through the nasopharynx, where it is conveyed by droplets of secretion either from active cases or carriers. The onset is acute with signs of a nasopharyngitis slight malaise headache and fever. It has been customary to differentiate the cases into various clinical forms or types. These are however artificial distinctions being really of no value and are apt to confuse a broad conception of the disease. They really depend upon the severity of the three stages of the infection and the virulence of the organism which determines the clinical predominance of each.

As the portal of entry is through the nasopharynx here will be found the initial symptoms. These may be slight and frequently pass unnoticed. This

*Chronic meningococcus meningitis* may be either a continuation of the acute form or through the development of productive lesions may be considered as complications or sequelae

(a) A purulent exudate continues in the rachnoid space for a prolonged period in spite of treatment. The temperature remains high and meningococci persist. The eventual outlook is favorable in adults unless mechanical or obstructive lesions develop. These are most common in infants and young children but do occur occasionally in older persons. It usually assumes the following form

(b) Chronic posterior basal meningitis. The exudate is thick and organizing chiefly over the basal areas, although it may cover the vertex as well. In the former situation it may lead to obstruction of either the interventricular foramina or the foramen magnum. Either of these conditions leads to an internal hydrocephalus with the usual signs of bulging fontanelles and cephalic ery. The head retraction and opisthotonos are progressive but the limbs instead of being flexed are extended and spastic. There may be a continuous pyrexia or it may recur after a short interval with leucocytosis. The spinal fluid may be clear and neither lumbar nor cisterna drainage is effective. Ventricular puncture reveals purulent fluid which contains meningococci, and temporarily relieves the pressure. The outcome is fatal in from six to eight weeks.

(c) In milder cases where the vertex is principally involved and the ventricular obstruction is not complete a more chronic state with all the signs of increased intracranial pressure may ensue. A fatal result is, however eventually to be expected.

The other metastatic lesions of this systemic infection are not numerous and consist chiefly of arthritis, iritis, choriorretinitis, pinophthalmitis, pneumonia, pleurisy, pericarditis and orchitis.

The complications or sequelae are the result of the local metastatic lesions and are therefore most numerous in the brain and cranial nerves. The occurrence of internal hydrocephalus and increased intracranial pressure have already been referred to. Closely associated with these are papilledema and optic atrophy. There may also be deafness, strabismus and signs of other cranial nerve lesions.

**Pathological Anatomy**—The anatomical changes are almost solely confined to the meninges and these depend to a large extent upon the stage at which they are examined. In the early stages—particularly in the fulminating septicemic cases the meninges may reveal no lesion. In similar cases with early nervous symptoms there is usually only hyperemia of the pia arachnoid and subarachnoid with edema and serous exudate. With the lapse of time the exudative process becomes more intense and profuse. There is greenish yellow fibropurulent exudate concentrated along the sulci particularly over the base and cerebellar areas. The parietal, occipital, and frontal lobes are irregularly involved. In the chronic stages the exudate becomes more fibrous and organized. Microscopic examination reveals no specific features. There is a progressive hyperemia and polymorphonuclear infiltration with many meningococci and finally fibrinous depositions which predominate in the chronic lesions. The ventricles are invaded by the inflammatory process and

tion and have no relation to the meningitis. They occur where the infection is purely a bacteriemia. At times the purpura may be so massive and deep as to lead to necrosis, and plaques of skin may be removed leaving an ulcerating area. From these necrotic patches the meningococci may be grown. The mucous membranes and conjunctivae may also be the site of these eruptions. They are more common in epidemics than in sporadic cases. Herpes about the lips and face occur in about 10 per cent of the cases, and appear usually between the fourth and seventh days. Splenomegaly is common and a pronounced leucocytosis is constant. It is of the polymorphonuclear type and may number up to 40 000 per cmm. Pyrexia ranges from 102° to 103° F but in the most severe and fulminating cases is seldom above 100° F. It is often accompanied by chills which are conspicuous when the bacteriemic stage is prolonged without meningitis. Vomiting would be expected when there is an increase of intracranial pressure, but it is prominent in this infection without such occurring.

The meningeal lesion is recognized not only by the characteristic symptoms and signs but more specifically by the changes in the spinal fluid obtained by lumbar or cisterna puncture. The fluid contains large numbers of polymorphonuclear pus cells which may or may not contain meningococci and these may be found free single in pairs or in small groups. Their early recognition is of the utmost diagnostic importance. They may not be found in stained smears of the fluid. It is imperative that cultures be made on proper media, the most favorable being, beef infusion peptone agar containing 1 per cent dextrose and 5 per cent defibrinated blood at a pH of 7.6 to 7.8. The cultures should be made immediately or the spinal fluid kept warm as the meningococci are particularly susceptible to cold. It is best therefore to make cultures at the bedside directly from the lumbar puncture needle when still inserted.

The relative frequency of the acute types varies considerably under different conditions. The regular type is the most common in epidemics as well as among the sporadic cases, although in the former these cases are on the average more severe and fulminating types increase in number as the epidemic progresses.

*Chronic recurrent meningococcus meningitis* really consists of one or more relapses. The patient recovers from the primary infection the spinal fluid being normal and then suddenly there is a return of fever and meningeal symptoms. These recurrences result from small pus pockets forming in the subarachnoid space which is otherwise clear, and they rupture leading to a repeated diffuse meningitis. The cause of their formation is not understood but it is probably due to an incomplete immunity or to poorly drained areas where the therapeutic agent has not ready access.

These recurring attacks are usually relatively mild and the infection is readily overcome with proper therapy. The intervals are usually a few days but may extend to weeks or months. There are seldom more than two. Occasionally a local productive lesion leads to internal hydrocephalus which for mechanical reasons is serious.



incidence is greater in the younger decades but the relative mortality is not parallel. The following comparisons from the Detroit epidemic of 1928-31 are instructive in this regard:

AGE	MORBIDITY IN CASES	MORTALITY IN PER CENT
0-4	33	38
5-9	44	40
10-14	186	36
15-19	133	43
20-24	107	50
25-29	110	50
30-34	43	60
35-39	38	64
40-44	43	50
45-49	29	80
50-54	2	70
55-59	7	100
60-64	4	100
65	3	0

Endemic and sporadic cases are relatively mild although startling exceptions are met with. The severity of the onset is not necessarily parallel to the future progress. In fact it is unwise to offer an opinion on the early severity of the disease. The most unfavorable features are early coma, convulsions or violent delirium and large purpuric areas as compared to petechiae. Early recognition and prompt treatment are of the utmost importance in prognosis in common with these same qualifications in all infections where a specific therapy is available.

The course of the disease has been indicated by the degree of the virulence, the type of the symptoms and the progress into the chronic anatomic meningeal lesions.

**Treatment.**—It may be taken for granted that all the usual measures indicated in an acute infection will be employed. For the central and peripheral symptoms of cerebrospinal irritation hydrotherapy is helpful. Warm baths with gentle friction bring about great relief as does at times an ice bag to the head. But the therapy of the greatest importance is specific and the earlier and more intensively it is used the greater are the hopes of success. This may be either by specific serum or chemotherapy. There is inherent in serum therapy a difficulty which is not sufficiently appreciated. In common with pneumococcal serum all preparations do not possess equal potency for each type of meningococci. There is little doubt that many of the failures in serum therapy are due to using a product which is not specific. It is regrettable that such is the case and that the specificity may not be more easily determined. Therefore a polyvalent serum has advantages although a more concentrated type specific serum would naturally give better results.

The sulfonamides (sulfadiazine or sulfamerazine) and penicillin have now practically replaced specific serum. They can be used either by mouth or intravenously (see Chapter XX) and have conspicuously reduced the mortality. It is not necessary to determine the type of the organism. In fact any purulent meningitis should be so treated promptly after a lumbar puncture has demonstrated its character and the causative agent determined later. This saves those first hours which are so precious for a successful result. Furthermore

distention is common at autopsy. The cortex may also be invaded as may the spinal cord as the lesion extends from the vertex to the cauda equina.

**Diagnosis**—The diagnosis is divisible into three phases. (1) *Carriers*—It must be appreciated that particularly in epidemics but also at other times persons may suffer from a mild and even negligible nasopharyngitis and hence harbor the meningococcus in the nasal and pharyngeal secretions. In fact these mild cases of nasopharyngitis without further symptoms may compose the majority of those infected, and many of these become carriers. They undoubtedly are an important factor in spreading the infection in epidemics. It would be expected that there would be some local lesion to allow the persistence of the organisms, but this is not clinically recognizable. These cases are most common in epidemics and among those exposed may number from 50 to 60 per cent, but the majority cease to be so in a few weeks' time. There are a small number who continue in this state. They can only be recognized by bacteriological methods, meningococci being found in cultures taken from the nasopharynx.

(2) The *septicemic phase* closely resembles other forms of blood infection except for the occurrence of the purpuric rashes. These, however, are common in other infections such as typhus fever, Rocky Mountain spotted fever, bacterial endocarditis, gonococcic, streptococcic and staphylococcic bacteremias, and the hemorrhagic forms of the exanthemata. Therefore a positive diagnosis can only be arrived at by blood cultures. In the fulminating cases death may occur before this is possible and consequently sporadic infections of this type are frequently overlooked.

(3) The *meningeal phase* is to be differentiated from other forms of meningeal infection which are dealt with below. In epidemics this is comparatively easy although occasionally a mistake is made through omitting to examine the spinal fluid. A lumbar puncture should be done immediately in all cases with the slightest suggestion of meningeal irritation. The technic of this procedure has already been dealt with. The examination of the spinal fluid gives the positive evidence of this specific infection. The cells are always polymorphonuclear and may number from a few to many thousands per cmm. This of course applies also to other pyogenic infections. The recognition of meningococci therefore is the sole means of making an absolute diagnosis. This may be accomplished by smears alone but cultures should always be taken to determine the type of meningococcus present.

The other meningeal lesions which may give difficulty in the differential diagnosis are influenzal meningitis in children, preparalytic poliomyelitis and meningismus in pneumonia, whooping cough, middle ear disease, mastoiditis, exanthemata and gastroenteritis. The examination of the spinal fluid usually clarifies the diagnosis except in those cases where organisms are not recovered in cultures. If there is a polymorphonuclear exudate it is best to give the meningococcus the benefit of the doubt.

**Prognosis**—There are a number of factors to be taken into consideration in prognosis. Of first importance is the age incidence. Patients under one year of age and over thirty withstand the infection relatively poorly. The

**Prognosis**—This is very serious the mortality being between 90 and 95 per cent

**Treatment**—The treatment has until recently been discouraging. Attempts have been made to produce antisera both bactericidal and antitoxic without much success in human beings. The introduction of sulfathiazole, sulfadiazine and streptomycin has ushered in an era of hope in the treatment of this disease (see Chapter XX).

### Tuberculous Meningitis

In Chapter VI when tuberculosis of the lungs was considered, mention was made of tuberculous meningitis. It is a metastatic lesion and in the majority of cases an old caseous focus will be found either in the lymphatic glands or the lungs. In some the infection can be definitely traced to a localized caseous area in the brain or meninges the relic of a long past blood infection. It may also be part of the distribution of a general miliary tuberculosis. It is more common in children than in adults.

**Symptoms**—The onset is as a rule rather insidious. There are commonly prodromata in the way of listlessness, headache, anorexia, irritability and loss of weight. After a period the headache becomes more intense and there may be a sudden increase of the disability with vomiting and pyrexia and not infrequently convulsions. Sleep is disturbed and the signs of meningeal irritation become apparent (see page 1065). The pulse is rapid, respirations slightly increased, the spleen may be palpable and the child may cry constantly.

In a few days to a week the clinical pattern changes from one of excitement to one of progressive apathy. The vomiting and headache subside but the opisthotonos and contraction of the limbs are progressive with an occasional cephalic crisis. The abdomen is retracted and firm. Signs indicative of cranial palsies develop such as irregular pupils, strabismus and optic neuritis. The apathy progresses into coma although convulsions are not infrequent. The eyes remain half open and the respirations are sighing with a progressive tachycardia although the body temperature may now be subnormal. Signs of paralysis become more extensive and may include the face and limbs.

In some cases particularly in adults the onset may be almost explosive in its suddenness and the course last but a few days. In others it may be quite prolonged extending into many weeks. These variations seem to be related to the severity of the infection and the distribution and extent of the lesion.

As in all cases with the slightest suggestion of meningeal irritation, a lumbar puncture should be done at once. In this infection there are distinctive features. The fluid is under abnormal pressure which should be recorded. It is usually clear but on standing in test tubes a fine veil like web or clot appears in a few hours. This is almost diagnostic. The cells may number up to 1000 or more and are practically all lymphocytes in contradistinction to pyogenic infections. The reducing substances are under 30 mg per cent the chlorides under 640 mg per cent and the proteins are increased. Tubercle bacilli are most easily detected by examining the clot mentioned above. This is floated on to a glass slide, allowed to dry and then fixed and stained.

this treatment can be carried out under conditions where repeated lumbar punctures would be difficult. It must also be appreciated that horse serum is a foreign substance in the meninges and is held by some to perpetuate meningeal irritation and dispose to chronic meningitis. Sulfonamides do not have this disadvantage.

General measures particularly indicated are absolute rest and prevention of external stimulation as far as possible. Particular care should be taken with the lumbar and cervical regions to avoid excoriation and infection. Sedatives are sometimes necessary and the best are chloral hydrate and bromides. Lumbar puncture serves this purpose as it also relieves the headache. When there are signs of increased intracranial pressure which are not relieved by this measure, intravenous glucose (50 per cent) injections control it temporarily.

The convalescence should be carefully guarded. The patient should be kept in bed for at least three weeks after all signs have disappeared and return to normal activity slowly and progressively.

**Prophylaxis**—All articles and bedding in contact with the patient should be sterilized and a minimum number of persons should be permitted inside the room in order that the number of possible carriers may be reduced. Those in attendance should live an isolated life and before they return to other duties it is well to ascertain by nasopharyngeal cultures whether they are free of meningococci. Masks have been advocated but are likely to give a sense of false security so that important measures like washing the hands after contact with the patient and allowing handkerchiefs to be contaminated are neglected. Strict medical asepsis is always to be enforced. Vaccines have been used to a limited extent and seem reasonable, but prophylactic injection of antimeningococcic serum is useless and has the disadvantage of sensitizing a person to horse serum.

Carriers when detected should be isolated until proved to be free of the bacteria by two successive negative cultures. The majority of carriers are usually allowed to leave quarantine after two weeks as it is impracticable to maintain large numbers longer. If a patient remains a carrier after his convalescence is completed, the family should be notified and all measures taken to promote his relative isolation within the home.

### Influenzal Meningitis

This is a meningitis caused by the *B. influenzae* of Pfeiffer and is undoubtedly part of a general bacteremia due to this organism. It is most common in children under two years of age. In fact it may be called a disease of infancy.

The onset is sudden with vomiting, stiffness of the neck, and pyrexia. The signs of meningeal irritation gradually develop and assume great intensity with hyperpyrexia, coma and convulsions. Metastatic lesions similar to those encountered in influenza sometimes occur (page 109). The disease is not particularly prevalent in influenza epidemics but occurs sporadically.

**Diagnosis**—The diagnosis rests entirely upon finding the bacilli in the spinal fluid which is usually cloudy and yellowish and contains about equal numbers of polymorphonuclear cells and lymphocytes. A positive nitrite reaction is quite significant.

**Prognosis**—The prognosis is always serious but with the methods of treatment described below, the prognosis is steadily improving.

**Treatment**—Treatment is of little avail unless the diagnosis is made early. This is accomplished by cisterna and lumbar puncture done at the same time and the spinal canal irrigated with normal saline. An even better method is to irrigate through double trephine openings well forward in the frontal area toward the vertex. With cisterna and lumbar puncture needles in position, the subarachnoid space is irrigated with normal saline first from the lumbar to the cisterna areas until the fluid is clear, and then from the trephine openings on either side to the cisternal outlet. Ventricular irrigation may also be necessary. The prevention of adhesions may be aided by the injection of air before the saline irrigation. Chronic adhesive meningitis leading to internal hydrocephalus accounts for certain of the deaths. As in the case of pneumococcal infections elsewhere sulfonamides (sulfadiazine) (see page 250) have practically replaced the use of specific horse or rabbit serum. This is to some degree unfortunate, because, although chemotherapy has been spectacularly successful there are occasional cases where the severe toxemia can be conspicuously reduced by specific serum. There are also instances where thorough drainage is definitely indicated.

### Streptococcal Meningitis

Meningeal infection with the streptococcus occasionally is found where no other clinical evidence of infection can be detected. As with the pneumococcus this invasion must take place through some occult portal of entry and is most probably carried by the blood stream but what factors determine their localization in the meninges is not known.

**Symptoms and Signs**—The symptoms and signs do not differ in any way from the pneumococcal form and the distinction rests upon bacteriologic findings in the spinal fluid.

**Prognosis and Treatment**—The treatment of streptococcus meningitis has been greatly improved through the use of penicillin and sulfadiazine. The primary source of the infection such as the mastoid should be treated if possible. At frequent intervals once or more a day, the spinal fluid should be completely drained off. This should be done slowly by drops and the lumbar puncture needle may be left in place for hours if necessary. Fluids should be forced and sulfonamides and penicillin given as outlined in Chapter XX.

### Secondary Meningitis

Meningitis is not an unusual complication or sequela to certain primary lesions. The principal local sources of such infections are the following:

Acute and chronic otitis, mastoiditis, facial and scalp erysipelas, septic scalp wounds, cellulitis above the angle of the mouth, suppuration in the orbit, nose, antrum, ethmoid, frontal and sphenoid sinuses, compound fracture of the base of the skull and infected emboli from the heart or suppurating pulmonary lesions such as a lung abscess and bronchiectasis.

In addition to these local sources meningitis may be a metastatic lesion in general infections such as typhoid fever, undulant fever, gonorrhea, diph-

Another method is to place a cover glass in a Petri dish and pour in sufficient spinal fluid to several millimeters' depth. In a few hours a similar clot will form on the cover glass which then is removed, dried, and stained. Guinea pig inoculation must sometimes be resorted to.

**Pathological Anatomy**—Tubercles and exudate are usually most abundant over the interpeduncular space, temporal lobes, the Sylvian fissures and the lateral surfaces of the hemispheres. They may also be found through the whole of the cerebrospinal system. Their detection in the choroid by ophthalmoscopic examination indicates a miliary lesion. The ventricles are always distended and tubercles may be very abundant on the choroid plexus. The lesion is typical of tuberculosis and may extend into the nerve tissue, particularly along the blood vessels producing an area of tuberculous encephalitis.

**Diagnosis**—The diagnosis rests upon the clinical findings and the peculiar changes in the spinal fluid, particularly the predominance of lymphocytes in the exudate. When the polymorphonuclear cells are numerous there may be confusion with influenzal meningitis. In cases of acute syphilitic meningitis there may also be difficulty as in both a lymphocytic exudate is present and there is high protein with relatively few cells. But here the reducing substances and the chlorides are normal or only slightly reduced and spinal fluid Wassermann is positive in 100 per cent of the cases.

**Prognosis**—This is extremely serious. A few cases have been reported as cured but they are so exceptional as to suggest a mistake in diagnosis although the introduction of streptomycin provides a ray of hope for the future.

**Treatment**—The patient should be kept as comfortable as possible with sedatives, analgesics and repeated lumbar puncture. Until recently no treatment was of any avail but now streptomycin (see Chapter XX) has given reason for encouragement. It should be given both intravenously or intramuscularly and by mouth. There is a danger inherent in its intrathecal use namely that it seems to cause a severe foreign body reaction in the meninges when given after this manner.

### Acute Syphilitic Meningitis

This will be referred to when syphilis is discussed as a disease, but was taken up in this chapter in greater detail under Cerebrospinal Syphilis (see page 1053).

### Pneumococcal Meningitis

Meningitis caused by the pneumococcus may occur quite independently of any other clinically detectable lesion although there must be some occult portal of entry. The onset is usually quite acute with all the classical signs of intense meningeal irritation. There is pronounced pyrexia, polymorphonuclear leucocytosis and prostration.

The cerebrospinal fluid rapidly becomes purulent with a greenish color. It is thickish containing much fibrin. The pneumococci are abundant and are readily detected in smears and cultures.

**Diagnosis**—The correct diagnosis depends upon the evidence found in the lumbar puncture fluid and must be arrived at very early in the course of the disease for any hope of successful treatment.

The cerebrospinal fluid is under slight pressure and contains lymphocytes which vary from a few hundred to several thousand per cmm. There is slight increase of the protein content. The fluid has always been sterile to ordinary culture methods, but a filterable virus has been recovered as mentioned above.

**Diagnosis**—The diagnosis rests between encephalitis, poliomyelitis, syphilitic meningitis, tuberculous meningitis and the meningeal lesions sometimes found in infectious mononucleosis (see Chapter XX). It may at first be difficult to make a clear cut diagnosis, but in a short time the condition is clarified by the prompt recovery of the patient.

**Prognosis**—The prognosis is good as the mortality is nil and there are no residual paralysis or mental changes. Treatment is symptomatic.

### Serous Meningitis

This is an indefinite clinical syndrome and is not clearly demarcated from its cause. It is sometimes called "sterile meningitis." It is a symptom rather than a disease entity. The characteristic findings are signs of mild meningeal irritation, increased intracranial pressure, irregular pyrexia and leucocytosis. The spinal fluid is rich in protein and there is a mild leucocytic reaction, but the fluid is always sterile.

The conditions with which this reaction is associated are usually traumatic or vascular. The more common ones are subdural hemorrhage at birth, cranial trauma (with or without fracture necessarily), cranial operations where there has been considerable removal of tissue with resulting cavity, cerebral thrombosis, infarction and edema as in nephritis, the nephrotic state and certain blood diseases and hemorrhagic conditions such as thrombocytopenic purpura, scurvy and hemophilia. It may also occur in cases in which there is infection within the skull itself such as in acute mastoiditis.

It would appear that the meningeal reaction is the result of bloody or serous collections between the dural layers and is an irritative response. The presence of pyrexia and leucocytosis are findings common to most visceral hemorrhagic extravasations or infarctions and are in no way specific to this condition.

**Diagnosis**—The diagnosis rests upon the appreciation of the probable etiology and the elimination of all other causes of meningeal irritation.

**Prognosis and Treatment**—The prognosis and treatment depend entirely upon the character of the primary lesion as the meningeal condition is of secondary importance and resolves spontaneously. Lumbar puncture may relieve the intracranial pressure and its associated symptoms but should be used with caution and a full appreciation of the original condition.

### Chronic Adhesive Arachnoiditis

**Definition**—Adhesions of the arachnoid and cystic collections of fluid simulating brain or cord tumor.

**Etiology**—This is often obscure but the condition sometimes follows injuries and is sometimes inflammatory in origin.

**Symptoms**—These are usually slow in onset and prolonged in course. The cystic collections of fluid often simulate tumors in their symptomatology.

theria, pneumonia, pertussis, influenza, malaria, actinomycosis, scarlet fever, rheumatic fever, syphilis, and the acute exanthemata

The bacteria most frequently found in these forms of meningitis are the streptococcus, staphylococcus, pneumococcus, diphtheria bacillus, typhoid bacillus, *treponema pallidum* and gonococcus

**Symptoms and Signs**—The symptoms and signs of meningitis due to these causes are similar to those in acute meningococcic infection. The anatomic pathway of the infection is usually obvious or the systemic infection has already been identified before the meningeal symptoms develop. In rare instances these may appear early and seem to initiate the infection.

The specific cause of the meningitis is proved by examination of the cerebrospinal fluid. The prognosis depends upon the virulence of the organism and massiveness of the infection. It is usually very serious. It must be appreciated that the finding of bacteria in the cerebrospinal fluid does not necessarily indicate a meningitis in a clinical sense. It is not unusual to recover organisms of low virulence and in scant numbers in the lumbar puncture fluid with little or no cellular reaction in cases of otitis media, mastoiditis, and meningeal thrombosis. This may be an anatomical but not a clinical meningitis and recovery is the rule.

**Treatment**—The treatment is the same as that outlined under Pneumococcic Meningitis. If specific drugs or sera are available, they should be used early and persistently.

### Acute Lymphocytic Meningitis

An exudate into the cerebrospinal fluid is almost a constant finding in acute anterior poliomyelitis and in acute encephalitis. During the first 24 hours or so the cells are polymorphonuclear but soon these are superseded by lymphocytes. This cellular reaction undoubtedly signifies a meningeal lesion mild though it apparently may be.

There have been reported during recent years in increasing numbers cases with meningeal symptoms in which there was a lymphocytic exudate in the lumbar puncture fluid. It has been variously called *acute aseptic meningitis* by Wallgren, *benign lymphocytic chorion meningitis* by Armstrong and Lillie, *benign meningitis* by Rivers and Scott and other synonyms, but probably the best designation is *acute lymphocytic meningitis*.

It has now been definitely demonstrated that this disease is due to a medium sized virus which has been found in the spinal fluid and blood during its acute stage. Furthermore antibodies have been demonstrated in the blood of patients on recovery. The disease has been transmitted to monkeys, guinea pigs and mice. House mice form a natural reservoir for direct or indirect human infection.

**Symptoms and Signs**—The onset is sudden with intense headache, epigastric and ocular pain, nausea and vomiting, pyrexia and signs of meningeal irritation such as stiffness of the neck and Kernig's sign. There is pyrexia from 100° to 104° F which is irregular and lasts for a few days. There is no paralysis and the reflexes are normal.



and involvement of the pyramidal tract are sometimes present. In cerebellar abscesses there may be slight or marked cerebellar signs. The pain will frequently be located in the occipital region and down the back of the neck and the neck may be stiff. Cranial nerve signs may occur from pressure on the brain stem. Abscesses in other locations will cause focal signs depending upon the structures involved. If the infection has not broken into the subarachnoid space, the spinal fluid will be clear, although its pressure may be raised. The cells may be slightly increased, but not more than 100 per cubic millimeter, and the protein content may be raised. When the infection has spread to the subarachnoid space the signs of meningitis will be present.

Brain abscess may occur as metastasis particularly from lesions of the lungs such as bronchiectasis and lung abscess. In these cases it is usually multiple and may create a most bizarre pattern of symptoms. The diagnosis of brain abscess is frequently very difficult and especially the differentiation of cerebellar abscess from acute labyrinthitis without intracranial complication. In acute labyrinthitis there is nystagmus to the opposite side past pointing to the side of the lesion with both hands and vertigo and falling to the side of the lesion. In cerebellar abscess the nystagmus is to the side of the lesion, the past pointing is also to the side of the lesion but only with the homolateral hand, and there is vertigo and falling to the side of the lesion. Past pointing is tested by having the patient raise and lower his arm in front of him. When it is lowered it should be made to touch the finger of the examiner held in front of the patient. After doing this several times with the eyes open the patient should then do it with the eyes closed but if it deviates to one or the other side as it attempts to touch the examiner's finger then past pointing is present.

Brain abscess should be suspected in all cases of otitic inflammation in which the condition does not progress satisfactorily or in which it is complicated by increasing stiffness of the neck, irritability, somnolence, pupillary changes, congestion of the retinal veins, pain in the homolateral side of the face and increasing headache. These symptoms may occur to a less degree in serous meningitis (see page 1077) complicating inflammation of the mastoid or labyrinth.

**Pathological Anatomy**—The infection that leads to the brain abscess is usually due to thrombophlebitis and not to direct extension. From the veins it breaks into the cerebral tissue and may also spread by the perivascular spaces to involve the meninges. Necrosis and polymorphonuclear infiltration take place and within three days compound granular corpuscles may be found. The acute abscesses spread without encapsulation but the chronic abscesses are well encapsulated and surrounded by an area of softening. The encapsulation is by connective tissue and not by glia. At a distance from the chronic abscess there is often perivascular infiltration with lymphocytes and plasma cells which is probably due to filtration of toxins but not of organisms. Although glia cells do not take part in the formation of the capsule they show degenerative signs in the neighborhood of the abscess.

**Prognosis**—Metastatic abscesses are usually multiple, and because of this and of the fact that the primary source ordinarily cannot be treated the

but the signs are likely to be less marked and more variable. In the brain the adhesions usually form at the base and cause hydrocephalus, increased intra cranial pressure, and sometimes cranial nerve palsies. The condition often exists in contact with inflammatory processes going on in bone, as in the mastoid cells. The involvement may be diffuse or local. In the cord, signs of compression are also manifested. There may be pain in the back and vague motor and sensory impairments, but the level of involvement is not as well defined as in tumor cases. On lumbar puncture there may be signs of block, and the use of lipiodol may be necessary to determine the level of the lesion.

**Prognosis**—Following operation partial or complete recovery usually occurs.

**Treatment**—Craniotomy or laminectomy with freeing of the adhesions and evacuation of the cysts.

### Other Types of Meningitis

Other organisms may also cause meningitis, but this occurs infrequently. *Bacillus typhosus*, coli, enteritidis, dysenteriae, anthracis, the virus of mumps, streptothrix, leptothrix and yeasts, such as *torula*, have all been described as etiological agents.

### Intracranial Abscess

**Definition**—Abscess formation in the epidural or subdural space or in the brain substance.

**Etiology**—The usual cause is spread of infection from the ears, mastoids or nasal sinuses. Metastatic abscesses also occur from sources at a distance, particularly from the lungs. The abscesses may be single or multiple (Fig 406). The bacterial cause will be the same as that of the primary infection.

**Symptoms**—The onset of symptoms may be insidious and the diagnosis difficult. It frequently follows suppression of discharge in a case of suppurative otitis media, operation on the mastoids or an acute flare up of an infected ear. The onset of symptoms may be acute or subacute. Headache, vomiting, malaise, slight fever and changes in the personality and sensorium are suggestive signs. The patient may grow irritable, have periods of drowsiness and of mental dullness. There may also be a polymorphonuclear leucocytosis in the blood. Signs of increased intracranial pressure may occur, but of these, headache may be the only prominent one. At first this may be paroxysmal but later it will become continuous and severe. Papilledema is often slight or absent. Slowing of the pulse is a common, but not constant finding. As pressure and toxicity increase there may be delirium and coma.

Epidural extension of the infection may cause no signs other than those already relating to the mastoiditis. Headache and tenderness of the side of the head may be noted. Extension beyond the dura from an ear or mastoid infection usually involves the temporal lobe or the cerebellum and in these locations, may not cause focal signs for some time. If the lesion involves the left temporal lobe in right handed people there may be some aphasia. Involvement of visual fibers passing through the temporal lobe may cause a quadrant hemianopsia to the opposite side of the body. Paralysis of ocular movements

involved nerve roots), sometimes herpetic eruptions in the same distribution and signs of compression of the spinal cord. The cord signs are usually paraplegia and sensory loss, up to the level of the lesion, and impairment of bladder function. The protein and cells in the cerebrospinal fluid are increased, and xanthochromia and From's syndrome (see later) may be present. The Queckenstedt test may show evidence of a complete or partial block. In cases of Pott's disease x-ray examination will show the typical changes in the vertebral column. The onset may be rapid.

**Pathological Anatomy**—There is obliteration of the extradural space with pus which becomes encapsulated. In the cord there is degeneration and there may be softening. In Pott's disease the characteristic changes in the spinal column are present.

**Prognosis**—This varies with the duration of the abscess and the damage to the cord. The condition is always serious but with relief of the compression the outlook is not hopeless and considerable, or even total recovery may occur.

**Treatment**—In Pott's disease the treatment is that ordinarily carried out for the spinal cord. In nontuberculous abscess laminectomy and drainage should be done.

## ENCEPHALITIDES

During the past thirty years much attention has been devoted after a modern fashion to a group of diseases which are probably much older than is usually appreciated. Among these may be included the following:

- 1 *Epidemic Encephalitis* (synonyms—encephalitis lethargica epidemic neuritis type 1 encephalitis [Japan] epidemic stupor 1 conomo's disease)
- 2 *Acute Disseminated Encephalomyelitis* (synonyms—postinfection encephalitis postvaccinal encephalitis postmeasles encephalitis acute perivascular myelinolysis)
- 3 *St. Louis Type of Encephalitis*
- 4 *Equine Encephalomyelitis*

All of these conditions show a strong clinical resemblance. The specific differential diagnosis rests entirely upon the history, the local occurrence of an epidemic or the isolation of a specific virus where known to exist. It is unfortunate that the term "epidemic encephalitis" was applied to one of this group because others also occur in epidemics but 3 and 4 above were not then recognized.

### Epidemic Encephalitis

**Definition**—An infectious disease of the central nervous system which may involve any part and so present diverse symptoms. A characteristic acute attack consists of lethargy and cranial nerve paralysis.

**Etiology**—The etiology of this disease is unknown. It is believed to be due to a virus and it presents the characteristics of an infectious disease. Males and females are about equally affected. It is most common in young adults.

**Symptoms**—As this disease may affect any part of the brain and in some cases even the cord and peripheral nerves the symptomatology varies to a

prognosis is bad. Single abscesses offer a better prognosis with surgical treatment, but even then the death rate is high. Spontaneous recovery occasionally takes place.

**Treatment**—The treatment consists of drainage after the abscess is localized. The primary source of infection such as the mastoid or lung should be dealt with first. The possibility of brain abscess developing in bronchiectasis or lung abscess is one of the important indications for early surgical interference in such conditions. If there is a gross tract of infection from the primary source to the brain abscess the latter can be drained at the same time. If such a gross path of infection does not exist then the abscess should be opened and drained through a clean field. Appropriate chemotherapy and/or antibiotic therapy should be employed as the bacteria found in these lesions are usually sensitive to their action (see Chapter XX).

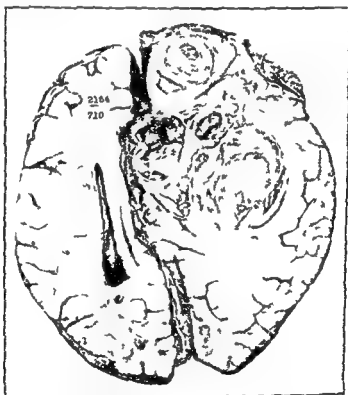


FIG. 406.—Multiple encapsulated cerebral abscesses.

### Extradural Abscess of the Cord

**Definition**—Intraspinal but extradural abscess causing compression of the spinal cord.

**Etiology**—Epidural abscess may be due to Pott's disease of the spine (tuberculosis) or secondary to a pyogenic infection elsewhere.

**Symptoms**—There are general signs of malaise and intoxication. The local signs are pain and tenderness of the back in the involved region. In Pott's disease there are in addition the signs of the spinal caries. Neurological manifestations consist of root pain (pains in the segmental distribution of the

that they must be institutionalized. Occasionally insomnia persists as a sequela and is sometimes manifested only at night whereas during the day time the patient is drowsy and lethargic.

2 Respiratory disorders. These are not common, but are a very definite sequela of epidemic encephalitis. They consist of marked dyspnea and slow noisy breathing. They are not associated with any impairment of body function or oxygenation of the blood.

3 Focal symptoms may persist when the disease has completely destroyed a part. These are usually paralyses of some of the muscles supplied by the third nerve. Occasionally, also muscles supplied by the bulbar nerves are paralyzed so that dysphagia or dysarthria may result. Tremors, choreiform movements, and torsion spasms also persist as sequelae or appear some times after the acute disease.

4 Paralysis agitans or the Parkinsonian syndrome is the most common sequela of encephalitis lethargica. Frequently an interval of years elapses between the acute attack and the appearance of the sequela, and in many cases the patient is unable to give a history of an acute attack. The symptomatology of this condition is discussed later in the section concerned with vascular diseases of the nervous system.

5 Oculogyric crises. Oculogyric crises are a sequela which became appreciated some years after the epidemic of encephalitis which occurred from 1918 to 1921. These crises consist of forced conjugate movements of the eyes usually in an upward direction. They occur at irregular intervals. Some times they can be precipitated by moving the eyes in different directions but in other cases there is no precipitating factor known. During the crisis the eyes will look upward and the patient will be unable to bring them out of that position. Less frequently forced lateral conjugate deviation and also downward movements occur. Some of these patients learn tricks by which to prevent or overcome this disability. Thus keeping on the hat so that its brim will shade the eyes will prevent attacks in some cases. In other patients attempts to read will bring the eyes back to a central position. The individual attack may last from a few minutes to an hour or more. These crises are frequently associated with other sequelae of this disease, particularly with the Parkinsonian syndrome.

6 Diabetes insipidus also occurs as a sequela of encephalitis. The symptoms and treatment of this disease are discussed on page 865.

7 Obesity follows in some cases. The diabetes insipidus and the obesity are probably due to involvement of the gray matter in the vicinity of the third ventricle.

**Pathological Anatomy**—The brain is hyperemic and congested. There may be hemorrhagic and inflammatory reactions in the meninges. Perivascular hemorrhages and infiltration with lymphocytes occur in the brain substance and are most frequent in, and often limited to, the midbrain and region of the basal ganglia. They may extend elsewhere. Cellular infiltration may extend beyond the perivascular spaces and be present in small foci in the brain substance. Degenerative changes are found in the nerve cells and in the walls of the blood vessels.

great extent. It may be divided into symptoms due to the general infection and symptoms due to the focal involvement. For some time previous to the manifestation of characteristic symptoms, the patient may complain of head ache, diffuse pains and some drowsiness. At the onset of the acute illness there may be fever but this is not usually high, may be intermittent and may persist for a long time. Headache, general malaise, vomiting and constipation also occur. Lethargy is one of the most characteristic symptoms. Ordinarily the patient can be aroused and will answer questions but will then immediately fall back into a sleep. Sometimes the lethargy is more marked and the patient sinks into coma. The facies is dull, smooth and apathetic. Mental symptoms may be present and at the onset of the disease they may be the only manifestation for some time. Depression, maniacal symptoms and schizophrenic symptoms have all been described. In addition, irritability, restlessness and sometimes delirium may occur. The cranial nerves are commonly involved and particularly the third nerve with the result that ptosis, strabismus, and diplopia almost always occur. There may be alterations in the pupillary reflexes with loss of the reflex to accommodation and with inability to converge the eyes on looking at a near object. Other cranial nerves are sometimes involved including the sixth and seventh and the nerves arising from the medulla. Abnormal movements are also a common symptom in this disease. Tremors, twitching, myoclonic movements and chorea and athetosis may occur. Sometimes hicough may be a very troublesome symptom. During the acute stage of the disease signs of paralysis agitans may be present, although these occur more commonly as a sequela. The reflexes may be altered and may vary from day to day and in some cases there is evidence of pyramidal tract involvement. Sensory loss is rare although pain and hyperesthesia do occur. Sphincter control is abolished in some cases either as an evidence of delirium or coma or because of loss of control due to focal lesions. Cerebellar signs and symptoms of cord involvement like those of anterior poliomyelitis occasionally are present. Sometimes a syndrome similar to myasthenia gravis occurs. Respiratory disturbances are sometimes present during the acute attack and sometimes occur as sequelae. These may be dyspnea, irregular respirations and deep sighing breathing. The cerebrospinal fluid is clear; it usually contains an increase in cells, ordinarily from 10 to 20 lymphocytes and rarely more than 100 per cmm. The globulin may be increased a little, the sugar is increased in contradistinction to meningitis in which it is decreased and some reduction of colloidal gold may occur.

**Course**—The course of the disease is variable. It may persist for a long time and relapses may occur. The sequelae of epidemic encephalitis are of great importance and of considerable interest. In many cases the sequelae overshadow the original attack which may have passed unnoticed. The more common sequelae are the following:

1. **Personality changes.** These are especially common in children and young adults. They consist of personality and conduct disorders and sometimes emotional and intellectual disturbances. It is common to find a child who was previously circumspect in every way become an habitual liar or thief. Frequently, also, they become quarrelsome, difficult to manage and cruel so

son recently vaccinated, may be given intravenously or intrathecally with great benefit. If this is not available, 10 c.c. of citrated whole blood may be given intramuscularly. In encephalomyelitis complicating specific infectious diseases, 10 c.c. of convalescent serum, obtained from a person who has had the disease within the previous year should be given intramuscularly or intravenously.

### St. Louis Type of Encephalitis

This type of encephalitis differs somewhat from the so called epidemic form although it may also occur sporadically or in epidemics. It is characterized by symptoms and signs referable to the meninges and cerebral nervous system.

**Etiology**—It is caused by a virus the mode of transmission being unknown although certain species of mosquitoes are suspected as experimental transmission has been effected by this means. In distinction from the epidemic form it is most prevalent in the summer months whereas the former is more common in the winter. Also although no age is exempt it occurs more frequently after forty five while the epidemic form is more usual before this age.

The virus is filtrable 20 to 70 millimicrons in diameter and can be transmitted experimentally through mice and rhesus monkeys. It can be grown only on media containing viable susceptible cells. A similar summer epidemic encephalitis has long been recognized in Japan. But this encephalitis differs from the St. Louis type on immunological grounds.

**Symptoms and Signs**—The onset may be abrupt or insidious. For this reason it has been customary to classify it into three groups. This hardly seems justified. With the acute onset there is early high fever, nausea, vomiting, headache, neck rigidity, vertigo and Kernig's sign, all of which would indicate an intense meningeal involvement. The signs indicative of central nervous system lesions are lethargy, slurred speech, difficulty, mental confusion and tremor of the tongue, lips and hands. Paralysis are not frequent and that of the eye muscles is rare. The deep reflexes however may be exaggerated with the abdominal reflexes absent. A bradycardia is sometimes conspicuous.

When the onset is insidious the temperature gradually rises over three or four days with other symptoms and signs of a general infection such as malaise, chilliness, sore throat, mild conjunctivitis and photophobia and generalized muscle and abdominal pains. Finally the meningo-encephalitic symptoms and signs appear similar to the cases with an acute onset.

The spinal fluid reveals the usual signs of meningeal involvement. It is under increased pressure, it contains a variable number of mononuclear cells, the globulin is increased, it contains a normal amount of sugar and no bacteria are found.

In an epidemic there are a fair number of quite mild cases which exhibit only some headache and moderate fever. Many of these are undoubtedly overlooked when they occur sporadically and even in epidemics unless a lumbar puncture is done.

**Pathological Anatomy**—On gross examination there are found edema, congestion and hemorrhages in the brain and spinal cord. The microscopic

**Prognosis**—When the initial attack is very acute death frequently results. The involvement of the medulla oblongata is serious because of the risk of cardiac and respiratory failure. The sequelae of the disease, or at least those which cause the greatest disability, are resistant to treatment. The prognosis therefore is always doubtful, inasmuch as these sequelae may not make their appearance until years after the original disease.

**Treatment**—There is no specific treatment for the acute attack. Isolation, nursing care, and symptomatic treatment are all of value. Personality changes and residual focal signs are usually permanent. Paralysis agitans may be improved a little but its treatment is disappointing. Diabetes insipidus can be well controlled by appropriate measures.

### Acute Disseminated Encephalomyelitis

**Definition**—An acute, toxic or infective disorder of the nervous system which may follow vaccination, certain of the acute specific infectious diseases (particularly measles and mumps) and other causes.

**Etiology**—The term comprises a group of nervous disorders, which seem to be increasing in frequency, but the ultimate cause and pathology of which are unknown. The condition occurs after vaccination, in conjunction with or immediately following most of the infectious diseases, after antirabic inoculation, and sometimes as a spontaneous disease the cause of which cannot be determined. It is unknown whether the involvement of the nervous system is due to actual invasion by the virus of the specific disease, to the action of toxins liberated elsewhere by these organisms, or to a specific virus which invades the nervous system and becomes pathogenic in the presence of these other diseases.

**Symptoms**—It is obvious that a disseminated inflammatory disease of such obscure etiology and pathology should manifest a multiplicity of different signs in different patients. The onset is usually acute, and headache and vomiting and fever are frequently present from the beginning. Drowsiness, stupor, delirium and coma may occur. Meningeal symptoms are present in many of these patients. There may be signs of widespread or focal damage to the central nervous system and these signs will depend upon the structures involved. Cranial nerve paralysis, optic neuritis, convulsions, monoplegia, hemiplegia and trismus may occur in different combinations. The cerebrospinal fluid may be normal or may be under increased pressure, contain an excess of cells and an increased amount of protein.

**Pathological Anatomy**—The brain is congested and edematous. There may be degeneration of ganglion cells and typical areas of focal demyelination, frequently arranged about blood vessels. Perivascular hemorrhages and infiltrations are common and there may be perivascular and pericellular edema.

**Prognosis**—The prognosis is variable both as to life and as to the persistence of focal residua. The mortality rate averages about 25 to 30 per cent but varies considerably.

**Treatment**—Repeated lumbar punctures and the use of hypertonic glucose saline solution may diminish cerebral edema and intracranial pressure. In postvaccinal encephalitis 10 c.c. of immune serum obtained from a per



be more insidious and much less violent. In all cases there are signs of meningeal irritation—rigidity of the neck and back and Kernig's sign. In children in usual edema of the face and arms is frequent.

The spinal fluid is under increased pressure and contains many cells up to several thousands. In distinction from other encephalitides the polymorphonuclear cells predominate up to 70 to 90 per cent. As is common to most types of encephalitis there is an increased protein but normal sugar content. A polymorphonuclear leucocytosis is almost constant.

**Diagnosis**—Diagnosis of an encephalitis is comparatively easy from the clinical aspect but the type is another matter. An epidemic associated with a similar outbreak in horses and/or mules is most significant but an absolute diagnosis can be arrived at only by the detection of the virus from brain tissue at autopsy. The specific causal diagnosis therefore usually rests upon inference.

**Course and Prognosis**—The course of those who recover is about ten days by lysis. But the mortality is high particularly in children as it has reached in the few epidemics reported up to 70 to 80 per cent. Death usually occurs in the first few days. The sequelae in those who survive are serious consisting of severe physical and mental deterioration.

**Treatment**—The prevention of the disease in an epidemic area can be resolved into measures to exclude the mosquito from contact with humans particularly children. There is no known specific therapy is yet therefore symptomatic measures are the only ones indicated. J. C. M.

### Diffuse Sclerosis

**Definition**—This term includes a variety of diseases of mixed degenerative and inflammatory nature. It includes *Schilder's disease* or *periaxial* encephalitis diffusa and also a group of familial cases described by Krabbe. The clinical findings and outcome are the same in the different types but the etiological factor is unknown. Whether the disease is due to a primary defect in nervous tissue or to a toxic or infective agent has not been determined.

**Symptoms**—The usual age of onset is before puberty although some cases develop later. Males seem to be affected more often than females. The characteristic symptomatology consists of blindness, mental deterioration, and spastic paralysis of the two sides of the body. The disease ordinarily begins in the occipital lobes and the resulting blindness is then not associated with pupillary changes or pathological manifestations in the fundi. When the temporal lobes are involved the result is deafness. Mental deterioration begins early and progresses and the bilateral spastic paralysis develops gradually. In some cases headache is a prominent symptom and sometimes disc changes are to be found although in typical cases the blindness is not associated with such changes.

**Pathological Anatomy**—The essential pathological condition is a symmetrical demyelination which usually begins in the occipital lobes spreads forward and is sharply circumscribed. Later in the disease the axones become swollen fragmented and destroyed. There are proliferation of fibrous astrocytes and

examination confirms these findings with infiltration of the meninges by lymphocytes plasma and large mononuclear cells with an occasional polymorphonuclear element. There is acute inflammation of the brain and cord showing congestion small hemorrhages, perivascular cellular infiltration degeneration of nerve cells and neuronophagia. Local collections of lymphocytes and glial elements are seen independent of the blood vessels.

**Diagnosis**—The diagnosis of a meningo-encephalitis is not one of great difficulty provided a lumbar puncture is done. The differentiation of the different types is however more difficult and cannot be accomplished with certainty by ordinary clinical methods. However complement fixation and neutralization tests are valuable aids in reaching a final diagnosis.

**Prognosis**—The mortality is about 20 per cent being higher in the upper decades than in children. If recovery occurs it is usually complete without sequelae.

**Treatment**—There is no known specific treatment. Therefore cases are best handled on symptomatic principles. T C M

### Equine Encephalitis

**Horses**—There seems little doubt that horses and mules in this country have suffered from a form of encephalitis for many years if not decades. It passed under a variety of names until its true nature was revealed by Meyer in 1931 when he demonstrated that a symptom complex was due to a virus and the disease was given its proper designation. In 1933 an epidemic of this disease occurred on the seaboard of New Jersey and Virginia which was demonstrated also to be due to a virus. This virus however was immunologically different from the western variety. Hence two forms of equine encephalitis are recognized namely the eastern and the western which are strictly separated by the Appalachian range.

It is now accepted that the virus may be transmitted by many species of mosquitoes which would account for its spread in local epidemics but not for its outbreak in distant areas. However it has been shown that birds (pigeons and pheasants) may require the disease and die of it as the virus has been isolated from these birds dying in their natural state. This could account for the distant spread of the disease. A perpetuating vector of the virus may be the tick *Dermacentor andersoni* which can harbor the virus and pass it on from one generation to another through the ova.

**Man**—There is no factual proof that the western variety has affected man. This was first suggested by Meyer who observed three patients with unclassified human encephalitis who had been in contact with sick horses but a viral cause was not proved in the patients or the animals.

In 1938 an epidemic of the eastern variety in horses occurred in Massachusetts with coincident appearance of an unusual number of cases of encephalitis in humans. These latter were proved to be due to the eastern virus which was isolated from the brains in the fatal cases.

**Symptoms and Signs**—These are in general the same as in other encephalitides. The onset in children is usually sudden with a high fever and frequent convulsions with rapidly progressive coma. In adults the onset may

syndrome of the albumino-cytologic dissociation (in which the patient usually recovered). Other synonyms are: acute febrile poliomyelitis, polyradiculoneuritis, infective neuritis, acute human infectious myelitis, polyneuritis with fibrin deposits, radiculoneuritis with cellular hyperalbuminosis of the spinal fluid (see above).

**Definition**—It will be noted that most if not all of these synonyms have little or no specific meaning. Therefore it is impossible to be concrete as to a definition except that there is a diffuse fibrin paralysis which may differentiate it from acute myelitis mentioned immediately above. In fact we are dealing with a potpourri of clinical and pathologic conditions.

**Etiology**—This is a complete mystery. It is well not to attempt at present even to suggest a general category. Infections of most diverse natures have been suggested, as have viruses, nutritional factors and chemical agents but they are all speculative.

**Symptoms and Signs**—The onset which may be preceded by a respiratory infection seven to fourteen days before is fairly sudden with fever, headaches, malaise and weakness to paralysis of the extremities. This may progress until the arms, legs and intercostal muscles are involved. The cranial nerves, particularly the seventh may also be affected. The paralysis is flaccid and the reflexes are diminished to absent. There may be sensory changes with hypo- and hyperesthesia to actual acute pain which is most distressing. Tingling and formication are common. It will be seen that the pattern is that of a lower motor neuron lesion of more or less symmetrical distribution.

In a certain number of cases there are also indications of meningeal irritation such as stiffness of the neck and Kernig's sign. The spinal fluid is under increased pressure. The number of cells usually mononuclear varies considerably from case to case. In some with signs of meningeal irritation they may number several hundred per cmm. In others they may be within normal limits but with a greatly increased protein content hence the term cellular hyperalbuminosis. A leucocytosis is often present.

**Diagnosis**—A specific diagnosis is often difficult. It is important to exclude anterior poliomyelitis, syphilitic myelitis, any or all of myeloencephaloides but even so the remainder present a conglomerate group. The importance of the diagnosis is more for estimating the possible prognosis than for any specific therapy.

**Prognosis**—The prognosis varies. Paralysis of the respiratory muscles will cause death. In many cases complete recovery follows beginning with return of function in the parts that were last paralyzed. The recovery is consequently a descending progression. The convalescence may last for months and sometimes residual weakness and muscular atrophy may remain.

**Treatment**—Absolute rest in bed is necessary and there is usually no other choice because of the paralysis. Contracture of the tendo achillis should be prevented by avoiding foot drop. When respirations are difficult the patient should be placed in the Drinker respirator. If sedatives are necessary morphine should not be given as this further depresses respiration. Atropine may prevent the accumulation of secretions in the upper respiratory passages.

the formation of compound granular corpuscles from microglia. Perivascular infiltration with lymphocytes and plasma cells varies considerably in intensity.

**Prognosis**—Death usually results within a period of two to three years and frequently within a few months. The disease is progressive but may show slight remissions.

**Treatment**—There is no treatment known.

### Myelitis

**Definition**—As the name indicates, this is an inflammatory disease of the spinal cord. It is frequently associated with more widespread inflammation and may then become meningomyelitis, encephalomyelitis or meningoencephalomyelitis. These terms indicate that the name is a combination of anatomical and pathological description, and that the condition is not specific as to etiology, course or prognosis.

**Etiology**—There is no specific etiology. Syphilis is a frequent cause of myelitis and this has been described under the heading of Syphilis of the Nervous System. Extension of infection either directly or through the blood stream may also be a cause. The term is loosely applied to softening following vascular occlusion or compression of the cord.

**Symptoms**—The onset may be acute or subacute and is sometimes associated with fever. The condition may be limited to a few segments, as transverse myelitis or it may involve many segments, as an ascending myelitis. The signs of involvement of nervous parenchyma will depend upon the site of the lesion and the structures which are involved. In transverse myelitis there is usually a spastic paralysis and some sensory loss up to the level of the lesion. Immediately above the lesion there is frequently a zone of hyperesthesia. Bladder function is sometimes impaired. In the ascending type of myelitis the paralysis may be of the lower motor neurone type from involvement of the anterior horn cells and their axones. The cerebrospinal fluid may contain an excess of protein and cells, and in syphilitic cases the Wassermann reaction is usually positive, although in many cases it is negative.

**Prognosis**—The prognosis varies depending upon the cause and the progression of the disease. Impairment of respiratory movement and infection of the bladder are serious.

**Treatment**—Symptomatic treatment, the care of the skin and the prevention of urinary infection are the chief indications during the disease. Potassium iodide may be used but its value is doubtful. If possible the cause should be treated.

### Acute Flaccid Paralysis

**Synonyms**—Under this symptomatic title may be grouped a wide variety of so-called clinical conditions. The confusion is not being clarified by the addition of more synonyms. Some ascribe to the role of separate conditions because the victim usually recovers, others because he usually dies, while in others the confusion is enlightened by definite sequelae which makes the diagnosis clear. It may be conceded that historically the first synonym was Landry's paralysis (usually fatal) then was enunciated the Guillain Barre

result. A form of poliomyelitis is described, in which not only are there lower motor neurone paralyses but there may be upper motor neurone symptoms or cerebellar symptoms in addition. The ascending symmetrical type has already been described under the heading of Acute Infectious Paralysis (see page 1085). The disease may not be confined to motor structures. Pain, muscle tenderness, and stiffness of the back and neck are almost constant features. Sometimes sensory impairment may occur from involvement of the spinothalamic tract by the process in the cord. The limbs are usually cold and blue.

**Sequelae**—Following the cessation of the acute illness, improvement begins to occur in the involved muscles. Usually, however, residual paralyses are left, and these are confined to restricted muscle groups, resulting in paralysis of certain movements such as flexion of the foot or abduction of the arm. Since only certain muscles in the limb are affected, contractures develop because of the unrestrained action of the antagonists. Deformities of the leg are common, such as talipes, and deformities of the spine such as scoliosis and kyphosis also occur. Bony growth may be retarded in the involved segment of a limb so that the corresponding segments on the two sides are not only unequal in girth but also in length. The residual paralyses are usually very much less in extent than the paralysis that existed during the acute illness, and it is always difficult to determine for some time just how much functional recovery will occur.

**Pathological Anatomy**—There are degenerative changes in the spleen, liver, kidneys and lymphoid tissue which becomes hyperplastic. The changes in the central nervous system are most marked in the anterior horns of the gray matter. There are hyperemia and dilatation of the blood vessels with perivascular hemorrhages and infiltration. The infiltration is usually of lymphocytes, but sometimes polymorphonuclear leucocytes are present as well. The infiltration extends beyond the perivascular spaces and may involve also the white matter and the meninges. The anterior horn cells show all degrees of degeneration to complete destruction and neuronophagia. Inflammatory changes may be present in the posterior nerve roots. Complete disappearance of motor cells in the anterior horn occurs and fibrous gliosis follows. Changes occur in the muscle tissue with atrophy and a relative increase of connective tissue and fat.

**Prognosis**—The prognosis varies in different epidemics and also depends upon the distribution of the lesion. Death has been reported in as many as 25 per cent of the cases in certain epidemics. This is sometimes due to paralysis of the respiratory center in the medulla and also to bronchopneumonia occurring in cases with paralysis of the intercostal muscles or diaphragm. The prognosis as far as sequelae are concerned may be difficult to determine. The preservation of faradic excitability in a muscle is of good prognostic significance as it shows that complete degeneration of the nerve supply has not occurred. Improvement may be slowly progressive over as long a period as a year. In some cases complete recovery takes place and this may even occur where very widespread paralysis existed during the acute illness. In other cases residual paralysis, contractures and atrophy remain and this disease is a frequent cause of crippling.

**Acute Anterior Poliomyelitis**

**Synonyms**—Infantile paralysis, Heme Medin's disease

**Definition**—An acute infectious disease which involves primarily the anterior horn cells and causes a lower motor neurone paralysis

**Etiology**—The cause of this disease is a filtrable virus which can be transmitted experimentally in animals and clinically in patients. The portal of entry has been in dispute. Some think it is the nose and nasopharynx with passage along the olfactory nerve. More recent opinion holds it is a water borne disease the virus having been found in the stools and in sewage. Further it has been shown that water and food may be contaminated by transmission of the virus by flies and mosquitoes.

**Incidence**—Anterior poliomyelitis may occur either sporadically or in epidemic form. It occurs in late summer and early autumn and usually disappears with the first frost. The incubation period has been variously estimated at from three to fourteen days. Males and females are about equally affected. Apparently the disease can be transmitted by healthy carriers or by the victims of abortive attacks in which there has been no paralysis. Most of the cases occur between the ages of two and four years, beyond that time there is a progressive diminution, although cases quite frequently occur in adult life.

**Symptoms**—The disease is an acute one and paralysis usually occurs within forty eight hours of the onset although in some cases it may be delayed for several days longer. The first symptoms are those of general systemic illness, headache, malaise, congestion of the throat, fever, and gastrointestinal symptoms such as anorexia, vomiting and diarrhea. These symptoms may last a short time only, and are usually associated with pain on movement of the legs and back. The muscles are tender and the neck and back are stiff so that attempts to flex them are painful. Kernig's sign may be present. Tremors may occur and convulsions are common at the onset in infants. At this stage the cerebrospinal fluid is under increased pressure and contains from 50 to 250 cells per c mm. The cells are at first both polymorphonuclear leucocytes and lymphocytes but within a few days the former disappear and only a few lymphocytes can be found. The protein and globulin are increased but the sugar and chlorides are normal. The disease may terminate at any time during the stages just described and paralysis may not occur. The paralysis is associated with pain and tenderness of the muscles. It may be widespread or local. In some cases all four limbs and the trunk may be involved at the same time. The distribution however, is usually more limited. It is asymmetrical on the two sides and may involve only certain muscle groups in a limb. The severity of the paralysis also varies in the different muscle groups. The maximum damage is done within the first twenty four hours but sometimes the paralysis is progressive for some days. The lower limbs are affected more often than the arms. The paralysis is of the lower motor neurone type with atrophy, flaccidity and absent tendon jerks. Improvement usually begins about the end of the first week and may continue for several weeks. Although ordinarily the legs are most affected the brunt of the disease may be borne by the brain stem and cranial nerve paralysis.

result. A form of poliomyelitis is described, in which not only are there lower motor neurone paralyses but there may be upper motor neurone symptoms or cerebellar symptoms in addition. The ascending symmetrical type has already been described under the heading of Acute Flaccid Paralysis (see page 1088). The disease may not be confined to motor structures. Pain, muscle tenderness and stiffness of the back and neck are almost constant features. Sometimes sensory impairment may occur from involvement of the spinothalamic tract by the process in the cord. The limbs are usually cold and blue.

**Sequelae**—Following the cessation of the acute illness, improvement begins to occur in the involved muscles. Usually, however, residual paralyses are left, and these are confined to restricted muscle groups, resulting in paralysis of certain movements such as flexion of the foot or abduction of the arm. Since only certain muscles in the limb are affected contractures develop because of the unrestrained action of the antagonists. Deformities of the leg are common, such as talipes, and deformities of the spine, such as scoliosis and kyphosis, also occur. Bony growth may be retarded in the involved segment of a limb so that the corresponding segments on the two sides are not only unequal in girth but also in length. The residual paralyses are usually very much less in extent than the paralysis that existed during the acute illness and it is always difficult to determine for some time just how much functional recovery will occur.

**Pathological Anatomy**—There are degenerative changes in the spleen, liver, kidneys and lymphoid tissue which becomes hyperplastic. The changes in the central nervous system are most marked in the anterior horns of the gray matter. There are hyperemia and dilatation of the blood vessels with perivascular hemorrhages and infiltration. The infiltration is usually of lymphocytes but sometimes polymorphonuclear leucocytes are present as well. The infiltration extends beyond the perivascular spaces and may involve also the white matter and the meninges. The anterior horn cells show all degrees of degeneration to complete destruction and neuronophagia. Inflammatory changes may be present in the posterior nerve roots. Complete disappearance of motor cells in the anterior horn occurs and fibrous gliosis follows. Changes occur in the muscle tissue with atrophy and a relative increase of connective tissue and fat.

**Prognosis**—The prognosis varies in different epidemics and also depends upon the distribution of the lesion. Death has been reported in as many as 25 per cent of the cases in certain epidemics. This is sometimes due to paralysis of the respiratory center in the medulla and also to bronchopneumonia occurring in cases with paralysis of the intercostal muscles or diaphragm. The prognosis as far as sequelae are concerned, may be difficult to determine. The preservation of faradic excitability in a muscle is of good prognostic significance as it shows that complete degeneration of the nerve supply has not occurred. Improvement may be slowly progressive over as long a period as a year. In some cases complete recovery takes place and this may even occur where very widespread paralysis existed during the acute illness. In other cases residual paralysis, contractures and atrophy remain and this disease is a frequent cause of crippling.

**Treatment**—A rigid anti infectious technic should be observed by all in contact with an acute case and all excreta should be promptly sterilized to prevent further pollution of sewage. During epidemics open air bathing should be prohibited, drinking water boiled, and all uncooked food carefully screened from flies. The administration of convalescent serum has been in use now for some years and the original optimistic reports are somewhat tempered; its value is questionable. Serum from a patient who has had anterior poliomyelitis should be given in the preparalytic stage of the disease, but this stage is extremely difficult and often impossible, to diagnose. From 10 to 25 cc of serum depending on the age of the patient are given intrathecally by gravity after removal of a slightly larger amount of cerebrospinal fluid. Another amount of serum, sufficient to make a total of 50 cc should be given intravenously at the same time. These injections are usually followed by a reaction and fever, and, if fever persists for more than twenty four hours, another 30 cc of serum should be given intravenously or intramuscularly. Hypertonic glucose saline may be given intravenously to reduce edema in severe cases. Hexamine in doses of 10 grains every four hours may be administered but its value is doubtful. When impairment of function of the intercostal muscles and diaphragm makes breathing difficult, the patient should be placed in the Dunlop respirator, and atropine may be given to diminish the secretions in the upper respiratory passages. Whereas in the past it was the custom to use splints to prevent contractures with massage and electric stimulation to maintain and increase the tone of supposedly paralytic muscles it is now held that every means should be used to relax the muscles as they are in a state of tonic contraction rather than paralytic. This requires careful handling under expert guidance. It is a revolutionary therapeutic approach introduced by Nurse Kenny. The essential features are keeping the joints in a neutral position, prevention of pressure, use of hot wet packs, all measures to improve the blood supply to the muscles and their re-education under skilled supervision. Swimming in a warm pool is of the greatest value.

### Synonym—Shingles

### Herpes Zoster

**Definition**—An acute infection of the posterior root ganglia with signs in the segmental distribution involved.

**Etiology**—The cause of this condition is probably a filtrable virus. It may occur with infections elsewhere in the body, particularly lobar pneumonia, malaria and meningococcal meningitis. It may also follow noninfectious lesions of the posterior roots such as injuries or tumors. It has been described in epidemic form and in close relationship to chicken pox. It is most frequent in middle aged or older adults.

**Symptoms**—At the onset of the illness and before the rash appears, there may be fever and pain in the side suggesting pleurisy. On the third or fourth day the rash comes out. It occurs in the segmental distribution of the nerve root involved and it forms papules and vesicles on a hyperemic skin. At first the fluid within the vesicles is clear but it frequently becomes purulent. In the involved area there are burning or shooting pains and hyperalgesia. The lymph nodes draining the area are enlarged. The vesicles may be superficial and heal without scarring, or they may be deep and cause disfiguring scars.



When the eruption subsides, there may be impairment of sensibility, but at the same time a persistence of the pain. Some of the cranial nerves may be involved in this process and, when the first division of the trigeminal nerve is affected, ulceration of the cornea usually occurs, and this may lead to loss of vision. The affection apparently may spread beyond the posterior root ganglia, and atrophy and weakness have been described in the segmental distribution, presumably from spread of the infection to the anterior horn cells. Signs of meningeal irritation may be present and there may be an increase in lymphocytes in the cerebrospinal fluid. Occasionally other complications occur. Postherpetic neuralgia may persist as a very troublesome sequela. The pain is in the distribution of the involved nerve roots and it is continuous, sharp and burning.



Fig. 40.—Herpes zoster in the distribution of the 6th and 5th cervical nerve roots and the 1st thoracic root.

**Pathological Anatomy**—There are acute hemorrhagic inflammatory changes in the posterior root ganglia and sometimes in the posterior gray horns of the cord, the posterior roots and the peripheral nerves. The condition is rarely bilateral. There is infiltration with mononuclear cells and with a few polymorphonuclear leucocytes arranged as perivascular cuffs. In severe cases the nerve cells show degenerative changes and secondary degeneration is present in the fibers. There are inflammatory changes also in the neighboring leptomeninges and in the skin.

**Prognosis**—Recovery usually occurs without complications except for some scarring of the skin. When postherpetic neuralgia follows, it may persist for years.

**Treatment**—The involved area should be covered with powder and a dry dressing. Iodatum and iodides have been used. Recently diphtheria antitoxin has been described as an effective remedy in this condition. It may be given in a dose of 5 000 units. It may be necessary to repeat this once or twice at intervals of 2 to 3 days. Convalescent serum may be given subcutaneously in doses of 10 cc. When postherpetic neuralgia occurs alcohol injection or

**Treatment**—A rigid anti infectious technic should be observed by all in contact with an acute case and all excreta should be promptly sterilized to prevent further pollution of sewage. During epidemics open air bathing should be prohibited, drinking water boiled and all uncooked food carefully screened from flies. The administration of convalescent serum has been in use now for some years, and the original optimistic reports are somewhat tempered, its value is questionable. Serum from a patient who has had anterior poliomyelitis should be given in the preparatory stage of the disease but this stage is extremely difficult and often impossible, to diagnose. From 10 to 25 cc of serum, depending on the age of the patient are given intrathecally by gravity, after removal of a slightly larger amount of cerebrospinal fluid. Another amount of serum sufficient to make a total of 50 cc should be given intravenously at the same time. These injections are usually followed by a reaction and fever, and, if fever persists for more than twenty four hours, another 30 cc of serum should be given intravenously or intramuscularly. Hypertonic glucose saline may be given intravenously to reduce edema in severe cases. Hexamine in doses of 10 grains every four hours may be administered, but its value is doubtful. When impairment of function of the intercostal muscles and diaphragm makes breathing difficult the patient should be placed in the Drinker respirator, and at opine may be given to diminish the secretions in the upper respiratory passages. Whereas in the past it was the custom to use splints to prevent contractures, with massage, and electric stimulation to maintain and increase the tone of supposedly parietic muscles it is now held that every means should be used to relax the muscles as they are in a state of tonic contraction rather than parietic. This requires careful handling under expert guidance. It is a revolutionary therapeutic approach introduced by Nurse Kenny. The essential features are keeping the joints in a neutral position, prevention of pressure, use of hot wet packs, all measures to improve the blood supply to the muscles and their re-education under skilled supervision. Swimming in a warm pool is of the greatest value.

### Synonym—Shingles

### Herpes Zoster

**Definition**—An acute infection of the posterior root ganglia with signs in the segmental distribution involved.

**Etiology**—The cause of this condition is probably a filtrable virus. It may occur with infections elsewhere in the body particularly lobar pneumonia, malaria and meningococcal meningitis. It may also follow noninfectious lesions of the posterior roots such as injuries or tumors. It has been described in epidemic form and in close relationship to chickenpox. It is most frequent in middle aged or older adults.

**Symptoms**—At the onset of the illness and before the rash appears there may be fever and pain in the side suggesting pleurisy. On the third or fourth day the rash comes out. It occurs in the segmental distribution of the nerve root involved, and it forms papules and vesicles on a hyperemic skin. At first the fluid within the vesicles is clear but it frequently becomes purulent. In the involved area there are burning or shooting pains and hyperalgesia. The lymph nodes draining the area are enlarged. The vesicles may be superficial and heal without scarring, or they may be deep and cause disfigurement, scars

paralysis may become complete. Other signs of alcoholism may be present, such as alcoholic dementia or Korsakoff's psychosis. In Korsakoff's psychosis there is an impairment of memory for recent events, but the patient disregards this and makes up for it by fabrication. The prognosis in alcoholic multiple neuritis is usually good although the illness may last for a very long time. Death from pneumonia or heart failure may occur during the illness.

**Lead Neuritis.** The widespread use of lead in paints, water pipes, etc., brings sources of intoxication within the reach of all. The neuritis which occurs may be associated with other signs of lead poisoning or with a previous history of lead colic. It involves the motor nerves almost entirely and rarely produces sensory changes. The paralysis is usually limited to the extensors of the wrists and fingers so that wrist drop is present. When the lower extremities are involved, it is chiefly the extensors of the foot which are affected and foot drop occurs. Further considerations in regard to lead poisoning are described under the heading of Lead Encephalopathy.

**Diabetic Polyneuritis.** This occurs usually in middle aged and older patients and it is possible that circulatory changes are partly responsible for the condition. The only evidence of the neuritis may be loss of tendon jerks and severe polyneuritis is exceptional. Sensory symptoms are usually prominent and the lower limbs are more affected than the upper. There may be considerable pain in the calves. Sometimes sense of position is lost, and the term 'diabetic tabes' has been used to describe the condition. This term should be discarded.

**Vitamin Deficiency.** Peripheral neuritis may occur due to a lack of vitamin B and the disease of beriberi is due to this cause. In addition, however, it is likely that certain other types of polyneuritis especially following the use of alcohol, are partly due to a deficiency of this vitamin. In beriberi the typical signs of peripheral neuritis are present and in addition, cardiac failure and gastrointestinal symptoms may occur.

Acute infective polyneuritis has already been discussed (page 1084).

**Pink Disease.** This disease is also known as erythroedema polyneuritis, trophodermatomyositis, aerodynia and vegetative neurosis (p. 794). It affects young children and is characterized by irritability, photophobia, reddish discoloration and swelling of the hands and feet and the symptoms of polyneuritis. Pathologically there is degeneration of myelin and chromatolysis of the anterior horn cells together with a diffuse infiltration with small cells. It occurs usually within the first year and a half of life and it has been regarded by some as infective and by others as a deficiency disease. The early symptoms are usually those of a mild infection of the upper respiratory tract or of the alimentary canal. Afterward the child becomes irritable, sleepless and loses his appetite. The hands and feet become bluish red, slightly swollen and cold. There is often an erythematous rash over the body and there is always excessive sweating and desquamation of the hands and feet. The rash is extremely irritative, trophic disturbances may occur, and analgesia, hypotonia and areflexia may be present.

**Diphtheritic Neuritis.** Neuritis may follow diphtheria of the ordinary type and has also been described after diphtheria associated with skin lesions but

section of the posterior root may not relieve the condition and section of the spinothalamic tract, which is conveying the pain fibers from the involved area, may be necessary. Deep x ray to the back in the region of the posterior nerve root should be tried before these surgical measures are undertaken.

### Neuritis

**Definition**—This term includes those lesions of the peripheral nerves which are due to inflammatory, degenerative or toxic processes.

**Etiology**—A wide variety of etiological agents exists. These may be divided into the following groups: (1) exogenous poison, such as lead and alcohol, (2) endogenous poisons, such as those of puerperal septicemia and intoxication, (3) metabolic and deficiency disorders, such as diabetes and vitamin deficiency, (4) infections, such as acute infective polyneuritis and diphtheria, (5) other causes, of which there are many.

**Pathological Anatomy**—The pathological changes may be perineural or interstitial, and are usually more marked at the periphery of the fibers. There are degeneration of myelin and proliferation of the sheath cells of Schwann, some of which become phagocytic. Changes in the axones may or may not occur. There may be an accumulation of lymphoid elements between the nerve bundles.

**Symptoms**—Neuritis may be local or diffuse and multiple. Constitutional symptoms will occur, depending upon the etiological factor. The symptoms of the neuritis are pain, impairment of power and impairment of sensation and these symptoms are present in the distribution of the affected nerve or nerves. The pain may be sharp, boring, stabbing, and is situated along the course of the nerve and in its distribution. Paraesthesiae, such as numbness and formication may be present. Frequently the nerve is sensitive along its course so that pressing upon it causes considerable pain. The impairment of function of the muscles is of a lower motor neurone type and may be partial or complete. Power, reflexes and faradic excitability will be diminished or absent and the muscles will be atrophied. Contractures may be brought about through the unhindered action of antagonists. All forms of sensibility may be impaired or lost. In some cases sensory findings are prominent, while in others they are completely overshadowed by the change in power and reflexes. Secondary effects may occur in the distribution of the nerve. The skin may be red or edematous; its temperature may be raised, and sweating may be excessive. Herpetiform eruptions and effusion into joints may also occur. Polyneuritis or multiple neuritis has a widespread and symmetrical distribution. It may be confined to the legs or may involve the arms and even the cranial nerves.

**Alcoholic Polyneuritis**—The amount of alcohol necessary to produce this varies considerably in different individuals. It is quite likely that the neuritis is not due entirely to the consumption of alcohol, but also to associated metabolic disorders or vitamin deficiency. It has been found experimentally that alcohol is capable of producing neurological manifestations much more easily in the presence of vitamin deficiency. Sensory disturbances are common in this type of polyneuritis and the muscles become very tender. The

except blood in the cerebrospinal fluid, and who develop normally and remain free from sequelae. On the other hand, it is likely that a considerable number of patients who develop epilepsy in their teens have suffered birth injuries of which there was never any evidence.

**Predisposing Factors**—The predisposing factors to birth injury are prematurity, prolonged or precipitate labor, disproportion in size between the head and the birth canal, the use of instruments and traction. Breech presentation is also a predisposing factor because of the traction that is necessary for delivery.

**Etiology**—The mechanical factors that cause the trauma are compression and distortion of the bony structures with resultant damage to the brain and cord, stretching or rupture of the spinal cord or of peripheral nerves from traction and compression or laceration of blood vessels and dura with circulatory changes following.

**Symptoms**—The signs and symptoms will depend upon the type of the lesion and its location. Damage to the bony structures alone does not give rise to neurological symptoms but such damage is often complicated by involvement of nervous structures. These complications are dural hemorrhage from dural tears and tentorial splits, subarachnoid hemorrhage from laceration or rupture of veins, and lacerations, contusions and hemorrhages of the brain and cord. When the blood is in communication with the subarachnoid space, the cerebrospinal fluid will be bloody.

**Pathological Anatomy**—Lacerations occur of the dural sinuses, the tentorium, the pia arachnoid, the brain and the spinal cord. With these there is hemorrhage which may be extradural, subdural, subarachnoid or within the nervous parenchyma. Contusion of the brain and cord with edema and widespread extravasation of blood may also be present. Actual rupture of the cord or nerve plexuses may occur. The subdural hematoma may organize and also the blood in the subarachnoid space may clot and organize in the arachnoidal villi or adhesions may form about the base of the brain. Within the brain and cord softening, necrosis and cavity formation or cicatrization may follow contusions and intracerebral hemorrhage.

**Sequelae**—Focal manifestations occurring with birth injury and described below are likely to persist. In addition certain end results may follow the pathological conditions described above. The obliteration of the arachnoid villi or the adhesions about the base of the brain may cause hydrocephalus (see page 1119). The widespread damage to the cortex may result in mental retardation. Convulsive attacks occur frequently either as evidence of focal or general cortical lesions. All these sequelae, except the last, develop progressively from the time of the injury but the convulsions may not begin until after an interval of many years. Retardation of growth of a part of the body may also result with a consequent inequality of the two sides.

**Prognosis**—The prognosis in these cases must always be guarded. With birth injuries sufficient to cause symptoms there is always the likelihood of sequelae and when focal signs are present from the start the prognosis is still more unfavorable. While much can be done with a child by education

with no faucial lesion Goodall reported, in a large series of cases of diphtheria, that 11.6 per cent showed palsy of some kind. Palatal palsy is the most common. Then in order come paralysis of accommodation, of the lower limbs, of the upper limbs, of the extraocular muscles, and of the larynx. About 1 per cent develop polyneuritis. The symptoms of neuritis ordinarily begin in two or three weeks after the original onset of diphtheria, but they may be delayed for as long as six months. The neuritis is manifested chiefly by weakness, but may be associated also with numbness and tingling in the extremities. Loss of position and vibration sense occurs quite commonly and these types of sensibility may become involved before those of touch and pain. There is no relationship between the severity of the diphtheria and the neuritis. Postdiphtheritic neuritis may last a long time, and in some cases the involvement of the nervous system may spread beyond the peripheral nerves and cause a plantar extensor response. Lesions have also been reported in the posterior columns of the spinal cord.

*Progressive Hypertrophic Interstitial Neuritis* This rare disease, which is frequently familial and characterized by an interstitial thickening in the peripheral nerves, is described on page 1050.

The signs produced by lesions of individual peripheral nerves are described on page 1107 under the heading of Peripheral Nerve Trauma.

**Treatment**—The treatment of peripheral neuritis consists of removing the source of the etiological agent, eliminating it from the body, correcting metabolic disturbances and treating the local condition. The involved muscles should be maintained in nutrition by physiotherapeutic measures, and contractures should be prevented or overcome. If there is no free hydrochloric acid in the stomach contents, one or two drams of dilute hydrochloric acid may be given well diluted with meals. Bed rest is necessary and the general health should be watched. A diet rich in vitamin B should be ordered, and if necessary this should be supplemented by administration of the vitamin in other forms. Massage, passive movements and galvanic stimulation should be carried out daily as soon as the patient can tolerate them. Analgesics and other drugs can be used when the symptoms indicate it.

## DISEASES DUE TO TRAUMA

Traumatic lesions of the nervous system may be sustained during the process of birth or at any time during life. The injury may involve the skull or vertebral column alone or it may cause damage to the nervous structures within, or to the peripheral nerves. Apart from the immediate effects of trauma there may be sequelae dating from the time of the accident or not becoming manifest until several years later.

### Birth Trauma

**Definition**—Trauma occurring to the child during the process of birth.

**Incidence**—Birth injury is responsible for more than one half of the deaths of viable babies and is the most important single cause of organic nervous disease in children with the exception of anterior poliomyelitis (Crothers). In addition it occurs in many babies who show no signs at birth.

The pulse may be slow or rapid. The efforts of crying and sucking are feeble. There may be rigidity of the neck, retraction of the head, and a bulging nonpulsating fontanelle. The pupils are dilated and usually unequal, with the larger pupil on the same side as the subdural bleeding. Hyperemia of the optic discs or papilledema and retinal hemorrhages may be seen. Convulsions occur and may be generalized or focal. Squints, nystagmus, hemiplegia and athetosis may be present and persist as sequelae (Fig. 408). The cerebrospinal fluid is under increased pressure and contains blood. It is often difficult to decide whether certain clinical findings are due to developmental defects or to birth trauma. Respiratory difficulty at birth and blood in the cerebrospinal fluid point to the latter cause. Developmental defects frequently produce characteristic syndromes, which have been described and the diagnosis is made easy when the signs in the particular case are typical. Infantile hemiplegia is usually the result of trauma while infantile diplegia usually results from a developmental defect. Microcephaly and microgyria, either unilateral or bilateral, may occur from either cause and sometimes follow a chronic subdural hematoma which prevents full growth of one side of the brain. Hematomata of the scalp and depressed skull fractures may follow the use of forceps.

### Cord Trauma

Injuries to the spinal cord usually result from traction exerted in breech presentations. The result may be fracture or fracture dislocation of the vertebral column and stretching laceration or rupture of the spinal cord. Meningeal bleeding occurs as described above. The damage if high in the cord, may cause death by paralysis of the phrenic nerves. In the stage of shock the cord lesion will produce a flaccid paralysis, sensory loss and loss of sphincter control. As shock wears off and improvement takes place the signs will become less marked and less widespread, and the sequelae will depend on the structures involved.

### Brachial Plexus Trauma

Brachial plexus palsies result from dislocation of the humerus and traction on the plexus during delivery. The distribution of the paralysis depends upon the direction of traction and upon the roots of the plexus which are injured. When the entire plexus is involved all the muscles supplied by it are paralyzed and atrophic and the arm is anesthetic. When the 5th and 6th cervical roots are involved an upper brachial plexus palsy or Erb's palsy, results. This is caused by traction of the head or twisting and depression of the shoulder. The muscles paralyzed are the deltoid, biceps brachialis and supinator longus and occasionally some other shoulder girdle muscles. The deformity is a typical one (Fig. 409). The arm and forearm are adducted and the forearm extended and pronated. Supination and flexion of the forearm and abduction and outward rotation of the arm are impossible. Atrophy of the involved muscles occurs but usually no sensory loss. A lesion of the 8th cervical and 1st dorsal roots causes a lower brachial plexus palsy or Klumpke's palsy. This occurs in breech presentations with an after coming arm where great traction is exerted. The resulting paralysis is in the muscles supplied by the

training and corrective measures, it is to be borne in mind that structures within the central nervous system, when once completely destroyed, will not regenerate

**Treatment**—When hemorrhage has occurred, the first consideration of treatment is the removal of the blood. In the case of subarachnoid bleeding, this can be done by repeated lumbar punctures, while if the bleeding has been epidural or subdural, the hematoma can be removed by operation. Areas of contused or softened brain should be removed so as to prevent the formation of a contracting cicatrix. It may be possible to treat the hydrocephalus by the methods described on page 1119. Epilepsy is treated by the removal of the focal cicatrix if one exists. Paralysis may require orthopedic measures as well as training and exercises. The feasibility of treating mental retardation will depend upon its degree, and the treatment will also consist of training and education. Many cases of birth injury are not recognized at birth nor until the child should be sitting up or even crawling or walking. The true state of affairs will then become apparent. Unfortunately in the past a gloomy outlook was taken by many and the child was considered as incurable. Fortunately this attitude is now rapidly disappearing and the spastics themselves are taking a hand in improving the lot of their fellow victims of these birth tragedies. A tremendous amount can be done in the way of physical education. The principal clue is to make a careful assessment of the probable assets and concentrate on these, but not necessarily to the total neglect of the deficits. On the other hand concentration on the latter to the neglect of the former is fatal. In many cases a great deal can be done to secure for them a useful and happy life with a high morale inherent in the fact of their being wanted.

### Intracranial Trauma

With intracranial injuries such as those described, the child may be born dead. If it is living there is usually respiratory difficulty with cyanosis slow and irregular breathing and death may follow from respiratory failure due to compression of the medulla and paralysis of the respiratory centers there.



Fig. 408.—Birth injury with infantile cerebral palsy. The lower extremities are in marked flexion and the infant is especially difficult to handle.



The pulse may be slow or rapid. The efforts of crying and sucking are feeble. There may be rigidity of the neck, retraction of the head, and a bulging, nonpulsating fontanelle. The pupils are dilated and usually unequal with the larger pupil on the same side as the subdural bleeding. Hyperemia of the optic discs or papilledema and retinal hemorrhages may be seen. Convulsions occur and may be generalized or focal. Squints, nystagmus, hemiplegia and athetosis may be present and persist as sequelae (Fig. 408). The cerebrospinal fluid is under increased pressure and contains blood. It is often difficult to decide whether certain clinical findings are due to developmental defects or to birth trauma. Respiratory difficulty at birth and blood in the cerebrospinal fluid point to the latter cause. Developmental defects frequently produce characteristic syndromes, which have been described, and the diagnosis is made easy when the signs in the particular case are typical. Infantile hemiplegia is usually the result of trauma while infantile diplegia usually results from a developmental defect. Microcephaly and microgyria, either unilateral or bilateral, may occur from either cause and sometimes follow a chronic subdural hematoma which prevents full growth of one side of the brain. Hematomata of the scalp and depressed skull fractures may follow the use of forceps.

### Cord Trauma

Injuries to the spinal cord usually result from traction exerted in breech presentations. The result may be fracture or fracture-dislocation of the vertebral column and stretching, laceration or rupture of the spinal cord. Meningeal bleeding occurs as described above. The damage if high in the cord may cause death by paralysis of the phrenic nerves. In the stage of shock the cord lesion will produce a flaccid paralysis, sensory loss and loss of sphincter control. As shock wears off and improvement takes place the signs will become less marked and less widespread and the sequelae will depend on the structures involved.

### Brachial Plexus Trauma

Brachial plexus palsies result from dislocation of the humerus and traction on the plexus during delivery. The distribution of the paralysis depends upon the direction of traction and upon the roots of the plexus which are injured. When the entire plexus is involved all the muscles supplied by it are paralyzed and atrophic and the arm is anesthetic. When the 5th and 6th cervical roots are involved, an upper brachial plexus palsy or Erb's palsy results. This is caused by traction of the head or twisting and depression of the shoulder. The muscles paralyzed are the deltoid, biceps, brachialis and supinator longus and occasionally some other shoulder girdle muscles. The deformity is a typical one (Fig. 409). The arm and forearm are adducted and the forearm extended and pronated. Supination and flexion of the forearm and abduction and outward rotation of the arm are impossible. Atrophy of the involved muscles occurs but usually no sensory loss. A lesion of the 8th cervical and 1st dorsal roots causes a lower brachial plexus palsy or Klumpke's palsy. This occurs in breech presentations with an after coming arm where great traction is exerted. The resulting paralysis is in the muscles supplied by the



Fig. 409—A child with an Erb's brachial plexus lesion produced during delivery. The left forearm is extended and pronated; the upper arm cannot be abducted and is rotated inward. (From Grinker, *Neurology*, Courtesy of Charles C. Thomas, Publisher, Springfield, Ill.)



Fig. 410—Fracture of the skull in the left parietal region.

ulnar nerve and inner head of the median nerve. Claw hand is produced by atrophy and paralysis of the small muscles of the hand. Sensation may be lost on the inner side of the hand and forearm in the distribution of the ulnar nerve or the 8th cervical and 1st thoracic roots. From paralysis of sympathetic fibers a Horner's syndrome results with perhaps also vasodilatation and absence of sweat secretion over the same side of the face. The Horner's syndrome is manifested by a small pupil, enophthalmos and slight ptosis.

### Postnatal Trauma

Trauma to the skull and vertebral column can be sustained by direct or indirect injury. A blow on top of the head can fracture the cervical spine and a severe fall on the feet when the body is rigid can do the same thing or even fracture the skull. From the standpoint of the neurologist a head or back injury becomes of importance when nervous structures are involved and their injury may be out of all proportion to the severity of the trauma suffered by the bones. Skull fractures (Fig. 410) may be simple, comminuted, depressed or compound. If they are basal they are more likely to be complicated than if they are vertical and in addition, they may be difficult to detect in x-ray films. Simple fractures require only rest in bed as treatment, whereas if depressions or dislocation of fragments are present they must be relieved by surgical measures. If the fracture line communicates with the paranasal sinuses infection of the meninges may further complicate the injury.

The vertebral column in the cervical region frequently suffers a fracture dislocation and such an injury is very liable to damage the spinal cord. Fractures may occur in other regions of the vertebral column as well but are much less likely to be associated with dislocation. The treatment of such injuries to the vertebral column consists of reduction by means of traction and hyperextension and fixation. By these measures it is possible to reduce the deformity very quickly but if actual destruction of cord tissue has occurred at the time of the accident this will not regenerate.

### Intracranial Trauma

At the time of the head injury the following complications may occur: concussion, contusion or laceration of the brain, subarachnoid hemorrhage, epidural or subdural hemorrhage with compression of the brain, and intracerebral hemorrhage. In addition there may be sequelae to the trauma in the nature of persistence of focal symptoms, posttraumatic headache and dizziness, posttraumatic epilepsy and personality changes.

**Symptoms.—Cerebral Concussion.** At the time of the accident the patient is rendered unconscious or consciousness is clouded. As he begins to recover he is dull and confused, may complain of headache and there may be nausea and vomiting. Memory is usually lost for the accident and there may also be a retrograde amnesia or a loss of memory for events preceding the accident. The pulse may be slow or rapid and thready and blood pressure may be lowered or slightly increased. The pupils may be dilated and if the shock is sufficient tonic and reflexes may be lost. The symptoms of the concussion

may be slight or they may be marked and associated with symptoms of other trauma to the nervous system. The recovery from concussion is ordinarily uneventful and rapid.

**Cerebral Contusion** With this there are capillary hemorrhages and edema of the brain. The patient is unconscious and may become more deeply so until death occurs, or he may slowly recover from the unconsciousness. The intracranial pressure is increased and the optic discs may be hyperemic and congested. The blood pressure may increase, and the pulse become slow, and frequent determinations of these are important. Headache, vomiting, confusion, and irritability become manifest as consciousness begins to return. Focal symptoms may occur as convulsions, cranial nerve palsies or paralysis of a limb or one side of the body.

**Cerebral Laceration** Laceration may occur directly from displaced bony fragments or it may occur because of the force of the injury. In the latter case the laceration may be at the site of the violence or directly opposite to it on the other side of the brain or contrecoup. There is an actual destruction of tissue with edema and hemorrhages surrounding it. The symptoms are like those of contusion, but focal symptoms are much more likely to occur and to persist.

**Subarachnoid Hemorrhage** Frequently with all types of head injury there is bleeding into the subarachnoid space from rupture of veins. This condition alone is not serious, although the associated conditions may be. The spinal fluid is under increased pressure and contains blood. If the bleeding is sufficient in amount there will be some stiffness of the neck and sometimes retraction of the head. Repeated lumbar punctures will diminish the intracranial pressure and also remove the blood. As the spinal fluid clears, the red blood cells gradually disappear from it and during this process the fluid is yellow.

**Epidural or Extradural Hemorrhage** This occurs from laceration of the middle meningeal artery or one of its branches. It may occur with or without a fracture and usually follows a blow in the temporal region. Following the initial injury there is unconsciousness from which the patient often recovers. After a lucid interval which may last several days, or which may be so short as to escape notice, there is a return to unconsciousness and signs of increasing intracranial pressure begin to appear. As the pressure slowly increases, it irritates visomotor and vagus centers and the blood pressure slowly rises while the pulse gradually becomes slower. When the pressure reaches the point where it begins to paralyze these centers the reverse occurs the blood pressure begins to drop and the pulse rate to rise. Respirations are at first slow and deep but then become irregular and may be of Cheyne Stokes character. In terminal stages they are rapid and shallow. With the increasing intracranial pressure unconsciousness becomes deeper and there is often papilledema. There may also be focal signs such as inequality in tendon jerks or in tonicity on the two sides, paralysis or convulsions of one side of the body or a plantar extensor reflex on one or both sides.

**Subdural Hemorrhage** This occurs from rupture of veins to the sinuses in the dura. The bleeding is slow and the signs are vague and may not attract notice until weeks or months have elapsed. Not infrequently the con-

dition may pass unnoticed for years. It may be very difficult to determine the side of the bleeding, and for this purpose the only localizing sign may be a homolateral dilated pupil. It may be necessary to trephine both sides of the skull to find the hematoma. The signs may simulate those of an intracranial tumor with slowly increasing intracranial pressure and vague localizing signs. Thus, gradual headache, drowsiness, confusion, and papilledema occur. The symptoms may fluctuate and hemiparesis, aphasia and sometimes ocular palsies may be present. A dilated and fixed pupil on the side of the lesion is common.

**Intracerebral Hemorrhage.** Intracerebral hemorrhage occurs in almost all severe head injuries. Small petechial hemorrhages in the brain substance and small subpial hemorrhages on the surface may remain discrete or unite to form larger hemorrhagic areas. Lacerations and contusions of the brain are associated with surrounding edema and hemorrhage. Depending upon the location of these areas focal signs may appear. Necrotic foci may also lead to posttraumatic sequelae due to healing by contracting scar tissue.

In head injuries the pressure of the cerebrospinal fluid is usually raised though occasionally it may be low. Blood is present in most severe cases and the supernatant fluid is yellow or xanthochromic. The red blood cells usually disappear in a few days but the xanthochromia may persist for a week or two longer. The protein is increased in proportion to the amount of blood in the fluid. If the intracranial pressure continues to rise the cerebrospinal fluid pressure will also increase. X-ray examination is of value both at the time of the injury and later. It will show the presence of fractures and plates taken after air injection will show displacements and distortions in the ventricular system from the pressure of dural hematomata and from the pull of contracting scars. Leaking of cerebrospinal fluid from the nose or ears is a serious circumstance, as it indicates damage to the intracranial contents and also affords a path for the entrance of infection.

**Pathological Anatomy.**—With injuries to the brain hemorrhages occur either from rupture of blood vessels or by diapedesis through their walls. These may be small petechial hemorrhages or larger ones caused by the fusion of several or by direct rupture of the vessels. Edema occurs around areas of contusion and laceration, and foci of softening and of degeneration and atrophy of the parenchyma are seen. Clean cut lacerations heal by a fine glial scar which is not contractile while necrotic areas and contusions made in connection with perforations of the dura heal with a contracting cicatrix containing connective tissue. Foreign bodies become encapsulated by mesenchymal and glial tissue. The scars which result may sometimes act as bacterial traps and infection may light up from them much later or following operative treatment. Old subdural hematomata become covered with a mesothelial membrane.

**Prognosis.**—This will depend upon the severity of the injury. Uncomplicated cerebral concussion and subarachnoid hemorrhage offer a good prognosis and are rarely fatal. Recovery from them is rapid. Contusions may prove fatal but ordinarily do not. In cases of compression of the brain by epidural and subdural hemorrhages the prognosis is not good and this in

particularly so if treatment is delayed. When infection is added to the other conditions, the prognosis is extremely bad. The likelihood of the development of sequelae cannot be determined by the severity of the original injury and the prognosis in this respect must always be guarded.

**Treatment**—The first requisite of treatment is rest in bed and even in cases of uncomplicated concussion this should be maintained for three weeks so as to diminish the likelihood of sequelae. The room should be darkened and quiet so as to prevent undue irritation. The patient should be kept warm and stimulants and analgesics should be given as indicated. Blood pressure and pulse rate should be determined at 15 or 30 minute intervals during the acute stage so that increasing intracranial pressure may be detected. If the intracranial pressure is higher than normal the head of the bed should be raised, if it is low, the head should be lowered. Repeated lumbar punctures will lower the intracranial pressure and also evacuate blood in the subarachnoid space (per cent solution) can be given by rectum or hypertonic glucose or sucrose saline space. To lower intracranial pressure magnesium sulphate (150 cc of 25 (50 or 100 cc of 50 per cent solution) can be given slowly intravenously. Depressed skull fracture and dural bleeding require operation, and softened cerebral tissue should be removed to prevent the formation of a contracting scar.

**Sequelae**—The question of sequelae of head injuries is one of considerable medicolegal importance. It is sometimes difficult to determine whether symptoms complained of are real or whether they represent a neurosis or a conscious effort to obtain compensation. This is particularly true of posttraumatic headache, personality changes and general disability not accompanied by abnormal physical signs.

Posttraumatic headache and dizziness form a syndrome which is well recognized at the present time. The headache is usually localized to the site of the injury and is a pressing or boring pain. Individual attacks of it may be induced by exertion and especially by such movements as stooping over. The duration of the attack varies and it is frequently accompanied by dizziness which is also made worse by stooping over. The dizziness may be a simple giddiness or an actual feeling of turning or of the movement of objects in the environment. Penfield believes that this is due to an abnormality of the leptomeninges following the trauma. Cinephalography sometimes shows evidence of this by the fact that air escapes from the subarachnoid space to the subdural space. If this cannot be determined in films taken immediately after the air injection it may become apparent in films taken one or two days later. The treatment of the condition is by the injection of air into the lumbar subarachnoid space or directly into the subdural space at the site of the headache. The head is then postured so as to move the air about in this location. It is believed that by this means small fine adhesions are broken down. Air is used instead of oxygen as it is more slowly absorbed. The relief is perhaps brought about through the breaking up of fine leptomeningeal adhesions and reopening of the subarachnoid space.

Posttraumatic epilepsy may follow birth injuries or injuries later in life. It may begin shortly after the accident or it may be delayed for as long as

ten years or more. The attacks are usually focal and the location of the lesion can, in a great many cases, be determined clinically by careful observation and consideration of the pattern of the attack. This question has been discussed on page 1006 in the section dealing with the cerebral cortex. If a sufficiently accurate description of the attacks cannot be obtained it is possible to induce attacks by hyperventilation or hydration (see page 1153) and to study them. Lucephalography is of great value in these cases as by means of it focal lesions in the brain may be indicated. Such lesions are meningocerebral cicatrices which have followed perforating wounds of the dura and contusion of the brain, and cerebral cicatrices and focal areas of atrophy. Foerster and Penfield have shown that scars forming in contused and softened brain tissue are contracting scars that they will exert a pull on the ventricles and so cause distortion and displacement of them. The part of the ventricular system which is nearest the scar is characteristically pulled in the direction of the scar and so the ventricular system is asymmetrical on the two sides. Areas of focal depression or atrophy of the brain can also be visualized because of the pooling of air about them. When posttraumatic epileptic attacks are focal in pattern and when objective evidence of a focal lesion in the brain is present removal of the focus offers a reasonable chance of cure. The removal is carried beyond the focal lesion into normal brain, and, as no softened or necrotic tissue is left behind the healing is by means of a thin noncontracting glial proliferation. If necessary, medical treatment is continued after the operation.

The use and value of electroencephalography are described in the section dealing with epilepsy.

Posttraumatic focal symptoms will persist in those cases in which there has been actual destruction of nervous tissue to cause them. The central nervous system does not regenerate although peripheral nerves can do so. Cranial nerve paralyses are particularly apt to occur and to persist in cases of basal skull fractures. The focal symptoms described above may persist if the damage has been complete.

Posttraumatic personality changes are particularly difficult to evaluate and to differentiate from neurotic symptoms and from symptoms complained of for the purpose of securing compensation. Easy fatigue, loss of initiative and ambition, irritability, impairment of memory and apprehension may be manifest and result in an inability to return to work. It is important in evaluating them to inquire carefully into the previous personality of the patient and his mode of reaction to difficult situations. Generally it is true that the clearing up of any litigation in connection with the accident is an important part of the treatment. In addition psychotherapy and, if necessary, the use of sedatives such as bromides and phenobarbital are also employed.

### Cord Trauma

As stated above damage to the spinal cord is particularly apt to occur with fracture dislocation of the cervical spine. Such an injury may follow direct violence or indirect violence such as a severe blow on top of the head. It is the type of injury which is often sustained by people diving into very

particularly so if treatment is delayed. When infection is added to the other conditions, the prognosis is extremely bad. The likelihood of the development of sequelae cannot be determined by the severity of the original injury and the prognosis in this respect must always be guarded.

**Treatment**—The first requisite of treatment is rest in bed and even in cases of uncomplicated concussion this should be maintained for three weeks so as to diminish the likelihood of sequelae. The room should be darkened and quiet so as to prevent undue irritation. The patient should be kept warm and stimulants and analgesics should be given as indicated. Blood pressure and pulse rate should be determined at 15 or 30 minute intervals during the acute stage so that increasing intracranial pressure may be detected. If the intracranial pressure is higher than normal the head of the bed should be raised, if it is low the head should be lowered. Repeated lumbar punctures will lower the intracranial pressure and also evacuate blood in the subarachnoid space. To lower intracranial pressure magnesium sulphate (100 cc of 25 (50 or 100 cc of 50 per cent solution) can be given slowly intravenously. Depressed skull fracture and dural bleeding require operation and softened cerebral tissue should be removed to prevent the formation of a contracting scar.

**Sequelae**—The question of sequelae of head injuries is one of considerable medicolegal importance. It is sometimes difficult to determine whether symptoms complained of are real or whether they represent a neurosis or a conscious effort to obtain compensation. This is particularly true of posttraumatic headache, personality changes and general disability not accompanied by abnormal physical signs.

Posttraumatic headache and dizziness form a syndrome which is well recognized at the present time. The headache is usually localized to the site of the injury and is a pressing or boring pain. Individual attacks of it may be induced by exertion and especially by such movements as stooping over. The duration of the attack varies, and it is frequently accompanied by dizziness which is also made worse by stooping over. The dizziness may be a simple giddiness or an actual feeling of turning or of the movement of objects in the environment. Penfield believes that this is due to an abnormality of the leptomeninges following the trauma. Encephalography sometimes shows evidence of this by the fact that air escapes from the subarachnoid space to the subdural space. If this cannot be determined in films taken immediately after the air injection it may become apparent in films taken one or two days later. The treatment of the condition is by the injection of air into the lumbar subarachnoid space or directly into the subdural space at the site of the headache. The head is then postured so as to move the air about in this location. It is believed that by this means small fine adhesions are broken down. Air is used instead of oxygen as it is more slowly absorbed. The relief is perhaps brought about through the breaking up of fine leptomeningeal adhesions and reopening of the subarachnoid space.

Posttraumatic epilepsy may follow birth injuries or injuries later in life. It may begin shortly after the accident or it may be delayed for as long as



with loss of sphincter control and the signs may increase in severity for a few days. It then comes to a standstill for a time after which improvement begins. As the lesion is usually chiefly in the grey matter, the residual symptoms are like those of syringomyelia (page 1136).

**Meningeal hemorrhage, epidural, subdural or subarachnoid,** may occur with trauma to the vertebral column and spinal cord. The symptoms vary depending upon the severity, the location, and the amount of compression exerted on the cord. Girdle pains or root pains may occur from pressure on posterior nerve roots and will be present in the segmental distribution of the involved roots. Compression of the cord will cause a level lesion with signs depending upon the severity of the compression. The cerebrospinal fluid will contain blood or blood pigment if the bleeding is in the subarachnoid space. Compression of the cord by a dislocation or a hematoma will produce signs of block in the cerebrospinal fluid circulation as described on page 1026.

**Pathological Anatomy**—The meninges may be torn by penetration of dislocated bony fragments and there is often meningeal bleeding. The cord substance may be completely or incompletely destroyed with necrosis softening and hemorrhages resulting. Connective tissue thickening of the dura and glial and connective tissue scarring of the cord occur. Secondary degeneration of the ascending and descending nerve tracts extends up and down the cord.

**Prognosis**—The prognosis depends upon the degree of destruction. With complete transection there will be no recovery and the prognosis for life is as bad as infection and death eventually occur. With incomplete transection residual signs will remain depending upon the structures destroyed. Paraplegia sensory loss and bladder disturbance also offer a poor prognosis. The signs of hematomyelia tend to improve and may leave only slight sequelae.

**Treatment**—In cases of dislocation of the vertebral column the treatment consists of reduction by traction and fixation. In dislocations of the thoracic and lumbar vertebrae hyperextension aids in the reduction. Bone grafting may be necessary in some cases to secure the fixation. In complete transection no other immediate treatment will help but in incomplete lesions operation may be indicated for the removal of foreign bodies. Care of the skin and of the bladder is necessary to prevent trophic disturbances and infections. Orthopedic treatment may be necessary in the treatment of the original injury and of sequelae.

**Sequelae**—Focal signs due to actual destruction of the cord will persist. Sometimes Kummel's disease may occur months after an injury to the back which may not be severe. In this condition there is softening of the bone and a spondylitis with ankylosis. Intercostal pain, pain in the back, and slight weakness in the legs may occur because of compression of nervous structures.

### Peripheral Nerve Trauma

**Symptoms**—Trauma to a peripheral nerve causes cessation of its function and produces motor sensory vasomotor and trophic disturbances in the area which it supplies. The weakness or paralysis is of the lower motor neurone

shallow water. In other regions of the vertebral column fracture dislocations may follow injuries which forcibly double up the individual or hyperflex the spine. Dislocations are less likely to occur with fractures of the thoracic or lumbar spine owing to the fact that they are more fixed and heavily muscled than the cervical region. Contusion of the cord may occur without gross injury to the vertebral column.

**Symptoms**—If destruction of the cord is complete, or if a great deal of shock accompanies the original trauma to the cord, the signs will be those of transection of the cord. All power, sensation, tonicity, and reflexes will be lost below the level of the lesion and there will be retention of urine and feces. If the transection has been complete, these signs will begin to change in about ten days or two weeks, and functions of the isolated cord will begin to return (page 1018). The establishment of these functions will take another two to three weeks. Tonus returns and stimulation of the soles of the feet or the skin of the legs causes a triple flexion mass reflex. At the same time automatic emptying of the bladder, and perhaps of the bowels, begins to be established, and the patient will void at intervals without being aware of it. Infection of the bladder eventually develops and thus ascends in the urinary tract and later causes a septicemia from which death results. If the transection has not been complete, the signs of shock will recede quickly and leave only the manifestations of the actual damage that has occurred in the cord. Thus pyramidal tract involvement may result in a paraplegia; sensory tract involvement in sensory loss, and the signs will be present from the level of the injury downward over the remainder of the body. With these impairments there is often disturbance of bladder function. The paralysis and sensory loss may be complete or incomplete depending upon the degree of damage and improvement may continue over a long period of time. If the lesion is high in the cervical cord, death usually results from involvement of the phrenic nerves and respiratory difficulty. If the level is at the 6th cervical segment, the adductors of the arm and extensors of the forearm are paralyzed so the arms become abducted and the forearms flexed. A lesion of the 7th cervical segment causes adduction of the arms and flexion of the forearms because of paralysis of the deltoid and triceps muscles. Involvement of the 8th cervical and 1st thoracic level causes a Horner's syndrome (see page 1017). Paralytic symptoms following cauda equina lesions are lower motor neurone in type. Their distribution and also that of the sensory loss will depend upon the roots involved. Usually bladder function is impaired and sexual power lost.

**Hematomyelia** or bleeding into the spinal cord may be caused by trauma or vascular or blood diseases. The trauma may be a direct one or an indirect one, and such bleeding may follow the general concussion of explosions. At the time of the injury the vertebral column may be injured or it may not and the hematomyelia may be associated with contusion of the cord or with meningeal hemorrhage. As with hemorrhage elsewhere in the nervous system the onset of symptoms is sudden. The artery involved is usually the anterior spinal artery or one of its branches. At the onset there is usually a paraplegia

Division of the musculocutaneous nerve causes marked weakness of flexion of the elbow joint, although the supinator longus may partly compensate for this. Sensation is impaired on the radial border of the forearm, as low as the carpometacarpal joint of the thumb.

With paralysis of the ulnar nerve the hands deflect to the radial side, adduction of the thumb is impossible, the first phalanges cannot be flexed, and the others cannot be extended. This may lead to a typical deformity called the "clawhand" in which the fourth and fifth fingers are extended at the metacarpophalangeal joint and flexed at the interphalangeal joints. The loss of sensation is over the little finger and the adjacent half of the fourth finger. Sometimes this anesthesia extends to half of the third finger over the back, and to the ulnar side of the hand.

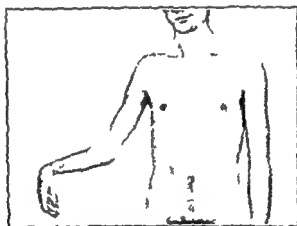


Fig. 431.—Wrist drop on the right side from a paralysis of the extensor muscles in a musculospiral nerve lesion.

The median nerve is rarely affected alone. The signs of involvement are inability to pronate the forearm beyond the midposition, deviation of the hand to the ulnar side when the wrist is flexed against resistance, and the thumb cannot be opposed to the tips of the fingers nor abducted when at right angles to the palm. The terminal phalanx of the thumb and the phalanges of the index finger cannot be flexed. There is weakness of flexion of the phalanges of the remaining fingers but not complete paralysis because the ulnar half of the flexor digitorum profundus is supplied by the ulnar nerve. Sensation is lost on the radial side of the palm and the front of the thumb, the first two fingers and half of the third finger, and the dorsal surfaces of the same three fingers.

In paralysis of the peroneal nerve there is foot drop and the foot cannot be dorsiflexed. Because of this when the patient walks he must raise the leg high from the ground in order to clear it, and this produces a characteristic gait. The loss of sensation is over the outer half of the front of the leg and on the dorsum of the foot.

**Treatment**—The treatment of these conditions consists of maintenance of muscle nutrition, prevention of contractures, removal of pressure upon the

type. Sensation is lost in the area of skin supplied and sometimes sympathetic phenomena occur. The trauma may be pressure, crushing, laceration or stretching. It may be mild, and followed by rapid recovery, or there may be complete section of the nerve with degenerative and regenerative processes going on within it (page 1020). While these are progressing simultaneous changes are going on in the muscles. Peripheral nerves to the arms and legs arise from plexuses which are formed by many nerve roots. In the plexus there is a rearrangement so that peripheral nerve distribution and segmental distribution are not identical. Consequently in lower motor neurone lesions and the sensory impairment associated with them, it must be determined whether the distribution is that of a peripheral nerve or of a nerve root. The distribution of a peripheral nerve may vary a little because fibers from one nerve may extend into the territory of another. For the innervation of muscles and the cutaneous distribution of peripheral nerves a textbook on anatomy should be consulted and it will be necessary to do so when the individual cases are being studied. A nerve may be involved in its distal portion and muscles supplied from more proximal levels will be intact. The symptoms which occur with lesions of the nerves most commonly involved are described below.

Lesions of the brachial plexus have been described under the heading of Birth Injuries on page 1096.

The posterior thoracic nerve is usually injured by a blow or prolonged pressure upon the shoulder. This nerve supplies the serratus magnus muscle which fixes the scapula to the chest when forward pressure is exerted with the upper limb and assists in elevating the arm above the head by rotating the scapula. When it is paralyzed there is no deformity while the arm is at rest but if the patient pushes the arm forward against resistance the scapula becomes markedly winged. In addition he is unable to raise the limb above the head in front of him.

The circumflex nerve which supplies the deltoid and teres minor muscles may be injured by lesions in the neck of the humerus. The results are wasting and paralysis of the deltoid muscle and marked weakness of abduction of the arm. In addition anesthesia and analgesia occur in an oval area extending from the acromial process halfway down the outer aspect of the arm.

The musculospiral nerve may be interrupted in the axilla and will then cause paralysis of extension of the elbow joint and paralysis of the supinator longus which will not contract when the forearm is flexed while in a position between pronation and supination. Paralysis of the supinator brevis leads to loss of supination. There is paralysis of the extensors of the wrist and fingers with a consequent wrist drop and finger drop (Fig. 411). Flexion of the fingers in gripping an object is also impaired because of absence of the synergic extension of the wrist which should occur with this movement. When the nerve is injured in the lower third of the arm as most frequently happens the triceps muscle will escape and the wrist drop and finger drop will be the chief disability.

The focal symptoms which occur in uncomplicated subarachnoid hemorrhage are usually due to cranial nerve involvement at the base of the brain. Associated with the subarachnoid hemorrhage, there may be hemorrhages into the retina, and sometimes slight papilledema.

**General Symptomatology**—Symptoms of general systemic disease, and of predisposing causes to vascular lesions within the brain, will be present when these exist. Inflammation about the ears or face which may lead to sinus thrombosis within the cranial cavity will present characteristic signs. Cardiovascular renal disease which is so often associated with cerebral complications and such blood diseases as purpura hemorrhagica and polycythemia will manifest the symptomatology which has been described elsewhere. Traumatic lesions and neoplasms of the brain are described under their own headings and will present their own signs. It is important, therefore, in vascular diseases of the nervous system to search throughout the entire body for predisposing or causative factors.

As indicated above aneurysms may be congenital or acquired. They may be arterial or arteriovenous, and they may or may not cause symptoms until hemorrhage occurs from them. When that happens the signs are those of subarachnoid hemorrhage. Symptoms occurring before rupture of the aneurysm will depend upon its size and location, and very frequently it is too small to make itself manifest. Sometimes headache, tinnitus, and bruits occur. The bruits coincide with systole, cause a throbbing rushing sensation and may be audible on auscultation of the head. These bruits occur particularly with arteriovenous aneurysms. Unless the aneurysm is very large, there will be no signs of increased intracranial pressure. Focal manifestations are usually those of cranial nerve involvement and with them there may be homolateral exophthalmos. X-ray examination may show some calcification in the wall of the aneurysm or erosion of the adjacent bone from pressure. In addition the injection of thorotrast may outline the dilatation (Fig. 413).

Cerebral hemorrhage, thrombosis and embolism may be impossible to differentiate from one another by clinical examination. Hemorrhage occurring as a sequel to trauma and located in the dural or subarachnoid spaces or in the brain is described under the heading of Trauma of the Nervous System. In subarachnoid hemorrhage the symptoms are those due to meningeal irritation and to focal involvement as described above. Crossed hemiplegia and bilateral pyramidal tract involvement may also occur. On lumbar puncture a bloody xanthochromic spinal fluid is obtained at the time of or after the hemorrhage. Intracerebral embolism, thrombosis and hemorrhage (Fig. 414) are of sudden onset. Sometimes vague premonitory signs may have been present before the hemorrhage or other complication occurred. Unconsciousness usually occurs at the onset although in cases of thrombosis this may not be so. In thrombosis also the signs may take from 24 to 48 hours to develop whereas in hemorrhage and embolism they occur immediately. These conditions occur chiefly in middle age and are associated usually with disease of the cardiovascular system. At the onset symptoms may be widespread because

In addition to hemorrhages, trauma may also cause arteriovenous aneurysms. Inflammatory lesions such as periarteritis nodosa, syphilis and others may cause aneurysms, thrombosis or embolus of the vessels. Tumors of the blood vessels, such as hemangiomas and hemangioblastomas, are also responsible for vascular lesions. Arteriosclerosis may be associated with cardiac and renal disease and may produce symptoms either of a diffuse character or focal manifestations following thrombosis or hemorrhage. In inflammatory diseases of the heart vegetations may become detached and form emboli in the brain. In purpura hemorrhagica and in polycythemia vera vascular changes may be produced in the brain. In the former disease hemorrhage may occur and in the latter thrombosis. Cerebral hemorrhage may be associated with cerebral tumor and occasionally the first evidence of the tumor may be caused by the hemorrhage.

**Pathological Anatomy**—The pathological mechanism of the production of lesions due to the causes named above, is described in Chapter VII. Cessation of circulation may occur during asystole in Stokes Adams disease. Vascular spasm within the brain is associated with fleeting clinical manifestations and may produce changes in the ganglion cells within the involved area. Hemorrhage may occur with or without rupture of vessel walls and may take place into the epidural, subdural or subarachnoid spaces or into the brain substance itself. Hemorrhage, thrombosis and embolus of cerebral vessels are accompanied by necrosis and softening of the brain tissue supplied by the vessels. Disturbances in innervation may produce prolonged vasoconstriction such as occurs in Raynaud's disease.

**Symptoms**—The onset of symptoms in cerebral vascular disease is usually sudden and the focal signs depend upon the location of the lesion. In chronic progressive diseases of vessels however such as arteriosclerosis and aneurysms slowly progressive symptoms may be found. When hemorrhage, thrombosis or embolus becomes associated with these diseases the onset of the symptoms which they produce is sudden. The symptomatology of epidural and subdural hemorrhage is discussed under the heading of Trauma of the Nervous System.

When subarachnoid hemorrhage occurs, the blood acts as an irritant to the meninges and the signs are consequently those of a meningitis with or without focal manifestations. The onset is sudden the neck is stiff the head may be retracted and there may be a positive Kernig's sign. Lumbar puncture yields a bloody spinal fluid if done early. As the blood begins to disappear from the spinal fluid the supernatant fluid becomes yellow in color and this xanthochromia persists for some time after all the red blood cells have disappeared. Subarachnoid hemorrhage may occur in young adults usually from rupture of a congenital aneurysm and it may also occur later in life from the same cause or from any lesion which will produce bleeding into the subarachnoid space. Intracerebral hemorrhages which break into the ventricles or into the subarachnoid space will also cause the appearance of blood in the spinal fluid.

of reaction and edema about the area primarily involved, but the neighborhood symptoms may rapidly clear and leave only the focal symptoms due to direct involvement.

The degree of cerebral arteriosclerosis that may exist need not necessarily be in proportion to that manifested elsewhere in the body. The neurological manifestations that are brought about are due to chronic progressive diminution in circulation and also to sudden vascular lesions usually of a thrombotic nature. The symptoms of cerebral thrombosis have been described above. The progressive ischemia may produce symptoms so slowly that they receive no special notice. These are progressive reduction in intellectual capacity, an impairment of memory particularly for recent events and some emotional instability. The memory for remote events is retained, and the patients spend much of their time in reminiscences about the past. There are likely to be personality changes also with the individual becoming self centered and disinclined to change his mode of life. Depression and delusions sometimes occur. The intellectual impairment may progress to the point of dementia when the patient becomes confused, disoriented and deteriorated. Tremor is present frequently in cerebral arteriosclerosis and paralysis agitans also occurs.

**Focal Symptomatology**—The principles of the anatomical diagnosis of nervous diseases have already been discussed in the section with that title, and some of the characteristic syndromes which occur have been described. Vascular disease and its acute complications hemorrhage, thrombosis and embolism, may occur any place in the central nervous system and so the focal signs may vary considerably. When a single vascular lesion will produce signs of involvement of different functional pathways, it must be located where those pathways meet in such a manner that their destruction will produce the signs manifested. This is well exemplified in the crossed paralyses which have already been described. When vascular lesions are diffuse or multiple the various functional pathways may be involved separately and in different locations. The most common location of vascular lesions of middle age is in the lenticulo striate artery which supplies the internal capsule. It has already been described how the motor pathways descend in the anterior part of this capsule and how sensory fibers ascend behind them. In addition the visual or optic radiations to the occipital lobes pass through the internal capsule posterior to the sensory fibers. A lesion in this location therefore depending upon its size may cause a hemiplegia on the opposite side of the body, a hemianesthesia on the opposite side of the body, a hemianopsia to the opposite side of the body or any combination of these three. Very frequently all three conditions obtain and they will be associated with aphasia if the lesion is in the dominant hemisphere. At the onset of a sudden hemiplegia tonicidity may be diminished and tendon reflexes absent but ordinarily within a few days these signs change to those typical of pyramidal tract involvement. At the onset of cerebral hemorrhage the coma may be so deep and shock so pronounced that diagnosis of the condition is difficult. In such cases the odor of the breath should be noted and urine and blood examined so that if uremia or diabetic coma is present, it may be adequately treated.





extend into the jugular vein in which case pressure on the neck will cause tenderness and the vein may even be felt as a hard cord. If infection involves the meninges there will be an increase of cells in the cerebrospinal fluid and these will be of the polymorphonuclear variety.

**Pathological Anatomy**—The pathological findings are those of thrombosis. There will be some organization and canalization of the thrombus. Hemorrhagic softening may occur in the superficial parts of the brain.

**Prognosis**—The prognosis is grave and the mortality rate is high.

**Treatment**—The source of infection must be treated and, in lateral sinus thrombosis surgical intervention should be carried out.

### Paralysis Agitans

**Synonym**—Parkinson's disease, or the Parkinsonian syndrome.

**Definition**—A chronic disease characterized by rigidity, tremor, slowness of movement and the impairment of certain so called automatic movements.

**Etiology**—The condition is a symptom complex due to lesions involving the corpus striatum or the substantia nigra and consequently it may be caused by various etiological agents. In young patients it is usually a sequela of epidemic encephalitis whereas beyond middle age it is usually associated with arteriosclerosis.

**Symptoms**—The disease may be bilateral or unilateral. Its onset is gradual and it frequently begins on the one side and then extends to the other. While the disease is named the "shaking palsy" in some cases tremor may be absent. The tremor may begin in one hand and then spread to involve the other, both legs and even the head. It is a slow tremor which is made worse by emotion and usually stops during voluntary movement but begins again as soon as the movement ceases. It has been called a "pill rolling" tremor because of the position of the thumb and fingers during it. The rigidity involves all the muscles of the affected part. It may become extreme. It is frequently of the cogwheel variety which is an intermittent relaxation and contraction as the muscle is passively moved. The generalized rigidity and impairment of movement cause a characteristic attitude on the part of the patient. The face is smooth and masklike, the eyes blink rarely and the expression does not change. As the attitude (Fig. 415) of the patient is usually one of flexion the eyebrows are elevated as he looks forward. The head and back are bowed forward and the arms are semiflexed at the elbows. Movements are slow and are particularly difficult to start. Thus a seated patient may take half a minute or more before he can initiate the movements necessary to stand up. Writing becomes impaired because of the tremor and rigidity and it is irregular, uneven and small. Movements are carried out en bloc so that in turning all segments of the body turn at the same time and slowly and with deliberation. In walking the patient takes short, slow, dragging steps and his body seems to be in advance of his feet so that he has difficulty some times in stopping. This is called *propulsion* and *festination*. In walking also the arms do not swing at the sides but hang motionless and rigid. *Propulsion*

**Prognosis**—The prognosis in these vascular lesions depends upon the site of involvement and the extent of involvement. Deep coma at the onset, and the persistence or increase of coma are grave signs. The question as to how many residual signs will remain cannot be answered for some weeks. Complete recovery may be made or focal symptoms may persist, usually those of hemiplegia or aphasia. Partial recovery may occur so that the patient is able to walk around and carry on a fairly active life, even though almost complete uselessness of the arm may persist.

**Treatment**—It is probable that rest in bed, and nothing more, is as effective as any more active measures. The general health should be watched. The patient should be changed in position from time to time, so as to prevent congestion of the lungs. The bowels should be kept free, and catheterization may be necessary. Diminishing intracranial pressure by lumbar punctures, bleeding, and the use of magnesium sulphate solutions by rectum have all been recommended, but their value is doubtful. If the patient is unconscious or if sensation is impaired great care must be taken in the use of hot water bottles, which may readily burn the skin. When the acute illness has subsided, passive movements, massage, and reeducation may help. The likelihood of further attacks must be kept in mind.

### Venous Sinus Thrombosis

**Etiology**—Thrombosis of the intracranial venous sinuses usually results from the extension of infection to the sinuses from neighboring structures such as the ears, nasal accessory sinuses or face. In addition it probably occurs rarely in marasmus and cachectic states in infancy and in old age.

**Symptoms**—In addition to the symptoms of the disease which is responsible for the thrombosis there are symptoms of septicemia and of defective venous drainage from the area of scalp adjacent to the sinus. The temperature is increased and irregular. The pulse is rapid and there may be rigors. Extension to the leptomeninges may cause signs of meningitis, and pulmonary embolism will cause pyemic abscesses in the lungs. There is mental dullness which may progress to delirium and vomiting and convulsions may occur.

In thrombosis of the cavernous sinus, there is edema of the optic discs, orbits, conjunctiva and face in the region of the eye. As the third, fourth and sixth cranial nerves lie in the wall of the sinus there may be ophthalmoplegia either partial or complete. Exophthalmos occurs because of the congestion and edema of the orbital structures. Pain is severe and felt in the region of the eye and forehead.

When thrombosis of the superior longitudinal sinus occurs there is a rise in intracranial pressure with headache, vomiting and papilledema occurring. There is usually retraction of the head and there are sometimes convulsions, squint, and bilateral pyramidal tract signs in the legs.

In thrombosis of the lateral sinus which usually follows infection of the mastoid, there is pain in the ear and swelling and edema of the scalp in that region. Delirium and vomiting occur and sometimes slight pyramidal tract signs will be manifest on the opposite side of the body. The thrombosis may

**Prognosis**—The course of the disease is slowly progressive and it may last for years. Of itself it does not interfere with life.

**Treatment**—Some improvement may follow the administration of hyoscyne belladonna or stramonium. Hyoscyne hydrobromate may be given in doses of gr  $\frac{1}{150}$  or  $\frac{1}{100}$  three times a day. If salivation is a prominent symptom tincture of belladonna minims 5 to 15, may be added. In some cases it is found that tincture of stramonium is more beneficial. This is started in doses of 10 minims three times a day and gradually increased until 40 to 60 minims are taken at each dose. Penzedrine sulfate in doses of about 10 mg morning and noon helps many cases also.

### Raynaud's Disease

**Definition**—Impairment of the circulation in the fingers and toes, which is usually symmetrical and accompanied by phasic color changes (116, 416).

The condition is due to vasoconstriction of the smaller arteries. Acrocyanosis in which the extremities are constantly blue and abnormally cold is a closely allied condition. These have been discussed in detail under Diseases of the Blood Vessels (Chapter VII). Patients with Raynaud's disease may develop symptoms of vascular spasm in other parts of the body especially in the nervous system and this may lead to transitory symptoms such as amblyopia, migraine epilepsy aphasia, hemiplegia etc.

### Hydrocephalus

Hydrocephalus is an increased accumulation of cerebrospinal fluid within the cranial cavity. It may result passively from atrophy of the brain or actively from an increased formation or deficient absorption, of cerebrospinal fluid. This fluid is formed within the ventricles leaves them by way of the foramen of Magendie and the foramina of Lushka circulates in the subarachnoid space and is absorbed primarily from the arachnoidal villi into the dural sinuses. There are two types of hydrocephalus an obstructive type and a communicating type. In the obstructive type fluid within the ventricles cannot get into the subarachnoid space because of an obstruction to its circulation. In the communicating type there is free communication between the ventricles and the subarachnoid space but there is a disturbance in the formation or the absorption of the fluid or an obstruction to the circulation within the subarachnoid space so that the absorbing mechanism cannot be reached.

It is possible that, if the pressure of blood in the veins draining the choroid plexus is increased excessive formation of cerebrospinal fluid takes place but if this is so it must be a rare occurrence. This mechanism has been used in part to explain the hydrocephalus that occurs in subtentorial tumors. It has been stated that displacement of the tentorium upward compresses the vein of Galen against the splenium of the corpus callosum, and so causes congestion in the choroid plexuses. But tumors in the same location also interfere with the drainage of the ventricles and this is the more likely mechanism

is also manifest when the patient is given a gentle push forward and has great difficulty in bringing himself to a standstill. On being pushed backward he may manifest retropulsion and may show lateropulsion as well. If the patient is seated in a chair, which is suddenly tilted from behind he will not throw up his legs in an effort to preserve his balance, as a normal individual would do. The voice becomes hesitant, monotonous and shrill, and there is often an initial retardation before speech can be started. In the type of paralysis agitans which follows encephalitis, there is usually excessive secretion of sebaceous material over the face and excessive saliva in the mouth. In addition, in this type, other sequelae of epidemic encephalitis may be present, especially oculogyric crises and sometimes dystonic movements.



Fig. 415.—Paralysis agitans. The arms and wrists are semiflexed, the body stiff and flexed forward. (From Grinker, *Neurology*, Courtesy of Charles C. Thomas, Publisher, Springfield, Ill.)

In young people who show the Parkinsonian syndrome after encephalitis, and who have the greatest difficulty in carrying out ordinary movements, there may be surprising agility when movements requiring greater volition are performed. Thus although he has great difficulty in walking, the patient may be able to run or swim well. In the same way, a patient who is almost immobile may display great agility in catching a ball which is thrown at him without warning.

**Pathological Anatomy**—There is degeneration within the striate body and the globus pallidus with atrophy and diminution in the number of large motor cells in this region. Large areas of degeneration may form lacunae which are macroscopically visible. Similar degeneration and atrophy of cells occur in the substantia nigra.

of the production of hydrocephalus in these cases. Obstruction to the flow of cerebrospinal fluid may occur at any point, but its most frequent locations are in the aqueduct of Sylvius in the subarachnoid space at the base of the brain or in the region of the Sylvian fissures. In the case of block of the aqueduct, obstructive hydrocephalus results whereas, when the lesion occurs at the level of the Sylvian fissure, free communication between the ventricles and the subarachnoid space exists and the hydrocephalus is of the communicating type. Obstruction may also occur at the foramen of Munro in which case the hydrocephalus will involve only one lateral ventricle.



Fig 41 —Hydrocephalus in a child. The head is enlarged and full in contour and the frontal bosses are bulging and prominent.

The obstruction may be due to congenital atresia of the aqueduct of Sylvius to adhesions following inflammatory lesions or to tumor growth. Congenital atresia of the aqueduct of Sylvius or of the foramina in the brain stem is sometimes associated with other congenital abnormalities such as clubfoot spina bifida or harelip. Defect in absorption may follow obstruction of the arachnoidal villi and their obliteration by the extension of inflammatory products in cases of leptomeningitis or of extravasated blood in cases of subarachnoid hemorrhage. The inflammatory product or the extravasated blood may then become organized leading to a permanent defect.

**Symptoms**—Hydrocephalus acquired in early infancy is associated with enlargement of the head which may become extreme (Fig 417). The sutures are separated and the fontanelle is enlarged and there is marked congestion of

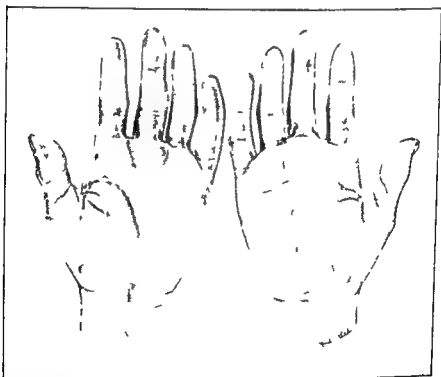
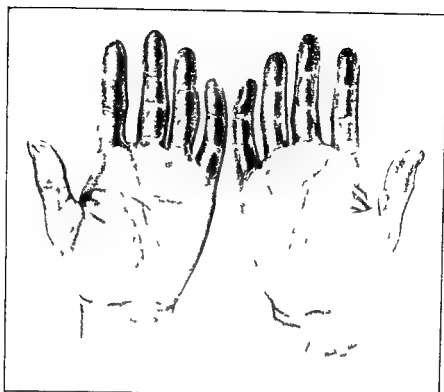


Fig. 416—A drawing of the physical changes in Raynaud's disease. Above, intense cyanosis of fingers fading in palm and absent above the wrist. Below, pallor of fingers tips. (From White: The Autonomic Nervous System, The Macmillan Company, New York, 1935.)

of the production of hydrocephalus in these cases. Obstruction to the flow of cerebrospinal fluid may occur at any point, but its most frequent locations are in the aqueduct of Sylvius in the subarachnoid space at the base of the brain or in the region of the Sylvian fissures. In the case of block of the aqueduct, obstructive hydrocephalus results whereas, when the lesion occurs at the level of the Sylvian fissure, free communication between the ventricles and the subarachnoid space exists and the hydrocephalus is of the communicating type. Obstruction may also occur at the foramen of Munro in which case the hydrocephalus will involve only one lateral ventricle.



Fig. 41.—Hydrocephalus in a child. The head is enlarged and full in contour and the frontal bosses are bulging and prominent.

The obstruction may be due to congenital atresia of the aqueduct of Sylvius to adhesions following inflammatory lesions or to tumor growth. Congenital atresia of the aqueduct of Sylvius, or of the foramina in the brain stem is sometimes associated with other congenital abnormalities such as clubfoot spina bifida or harelip. Defect in absorption may follow obstruction of the arachnoid villi and their obliteration by the extension of inflammatory products in cases of leptomeningitis or of extravasated blood in cases of subarachnoid hemorrhage. The inflammatory product or the extravasated blood may then become organized leading to a permanent defect.

**Symptoms**—Hydrocephalus acquired in early infancy is associated with enlargement of the head which may become extreme (Fig. 417). The sutures are separated and the fontanelle is enlarged and there is marked congestion of

the veins of the scalp. In extreme cases the head may be translucent and may yield a thrill and a murmur. Ordinarily the frontal region bulges forward and the eyes may be pressed forward and downward. Because the skull can expand, signs of increased intracranial pressure are not conspicuous but they may be present. Convulsions commonly occur. Papilledema or optic atrophy, or both, may be present and vision may be lost. Frequently strabismus and nystagmus are present. Usually there are weakness and incoordination of the limbs more marked in the legs than in the arms. Spasticity with increased reflexes, or absent reflexes, may occur. The plantar responses are usually extensor. The mental state varies and there is usually little or no disturbance in sensibility.

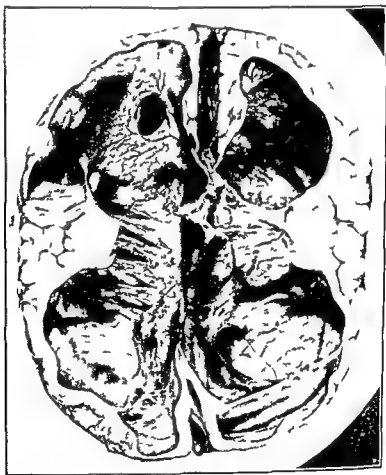


Fig. 418.—Tremendous internal hydrocephalus with distortion and thinning of the brain and dilatation of the ventricles.

When hydrocephalus is acquired in later life, signs of increased intracranial pressure are conspicuous. Headache, vomiting and papilledema occur and optic atrophy and blindness follow. Clouding of consciousness and intellectual deterioration may be present in advanced cases. Before the age of eighteen years there may be slight separation of the sutures and a cracked pot note, but after the age of eighteen enlargement of the head does not occur. Frequently, especially in children, there is venous congestion of the scalp.



Cranial nerve paralyses, especially of the sixth nerve exophthalmos clumsiness and incoordination and changes in the reflexes may be present.

X ray examination may show separation of the sutures convolutional markings thinning of the bones erosion of the clinoid processes and deepening of the sella turcica. If the hydrocephalus is of the communicating type roentgenograms taken after the injection of air into the lumbar subarachnoid space will show the presence of dilated ventricles. If however the hydrocephalus is obstructive such air will not enter the ventricles and the site of the obstruction may be apparent. In obstructive hydrocephalus air injected directly into the ventricles will show dilated ventricles often to an extreme degree so that only a thin layer of cerebral tissue remains. If dye is injected into the ventricles and can later be obtained from the subarachnoid space the hydrocephalus is apparently of the communicating type. If on the other hand the dye cannot be recovered the hydrocephalus is obviously obstructive in nature. Furthermore in obstructive hydrocephalus the pressure of cerebrospinal fluid in the ventricles differs from that in the subarachnoid space in the lumbar region, whereas in communicating hydrocephalus the pressure is the same in the two locations and is raised.

In addition to the signs of the hydrocephalus there will be signs also of the lesion which is causing it particularly if this is a cerebellar or brain stem tumor.

**Pathological Anatomy**—There are dilatation of the ventricles and thinning of the hemispheres (Fig. 419) with some atrophy of the cortical ganglion cells. The cause of the obstruction presents its own pathology.

**Prognosis**—Most cases of congenital hydrocephalus prove fatal within the first few years of life. The prognosis in acquired cases depends upon the cause and how amenable it is to treatment.

**Treatment**—This consists of removing the cause of the hydrocephalus or destroying the choroid plexus by cautery or by removal or of providing a new outlet which will allow spinal fluid to reach the absorbing surfaces of the arachnoidal villi. To bring about the last it may be possible to dilate the aqueduct of Sylvius or to make a new foramen of Magendie or to puncture the corpus callosum or amputate the anterior pole of the temporal lobe. To diminish the increased intracranial pressure before operation lumbar puncture can be carried out in cases of communicating hydrocephalus fluids can be restricted and hypertonic glucose saline solution can be given in either type of hydrocephalus. Treatment however is unsatisfactory.

## TUMORS OF THE NERVOUS SYSTEM

Tumors of the nervous system may be primary or secondary (metastatic). The term is used here to include the infective granulomata due to tuberculosis and syphilis. The tumors may be located in the bones of the skull or vertebral column in the meninges in the blood vessels or in the nervous tissues of brain cord or peripheral nerves. They may be benign or malignant. Primary tumors of the intracranial and intravertebral structures do not metastasize elsewhere in the body but in some cases they may metastasize from one area of

the veins of the scalp. In extreme cases the head may be translucent and may yield a thrill and a murmur. Ordinarily the frontal region bulges forward and the eyes may be pressed forward and downward. Because the skull can expand, signs of increased intracranial pressure are not conspicuous but they may be present. Convulsions commonly occur. Papilledema or optic atrophy, or both, may be present and vision may be lost. Frequently strabismus and nystagmus are present. Usually, there are weakness and incoordination of the limbs more marked in the legs than in the arms. Spasticity with increased reflexes, or absent reflexes, may occur. The plantar responses are usually extensor. The mental state varies and there is usually little or no disturbance in sensibility.

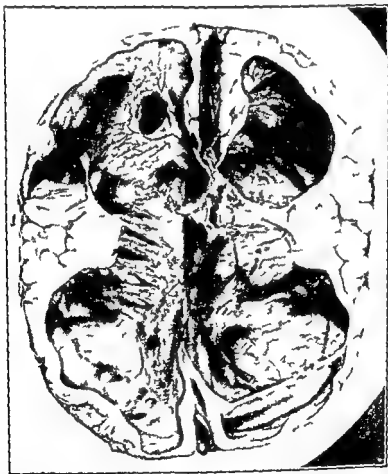


Fig. 418.—Transverse internal view of the brain with distortion and thinning of the brain tissue. Illustration of the ventricles.

When hydrocephalus is acquired in later life signs of increased intracranial pressure are conspicuous. Headache, vomiting and papilledema occur and optic atrophy and blindness follow. Clouding of consciousness and intellectual deterioration may be present in advanced cases. Before the age of eighteen years there may be slight separation of the sutures and a cracked pot note, but after the age of eighteen enlargement of the head does not occur. Frequently, especially in children, there is venous congestion of the scalp.

quently leads to paralysis of one or both sixth nerves with consequent paralysis of external rotation of the eye or eyes and convergent strabismus (Fig. 419)

Convulsions beginning in adult life must be regarded as due to structural change in the central nervous system unless proved otherwise. These convulsions may be general but are usually focal and are referred to under the heading of Focal Symptomatology. Mental disturbances occur in brain tumors but it is surprising how indistinct a relationship there is between the location of the tumor and the type or degree of mental disturbance. These symptoms occur more prominently in frontal and temporal lobe lesions, in tumors of the corpus callosum, and also in cerebellar tumors, in which they frequently do not appear until after the removal of the tumor or the release of the increased intracranial pressure. The mental symptoms are usually those of intellectual deterioration. There are some confusion, impairment of memory, inattentiveness, loss of initiative and dullness and late cases may go on to stupor.



Fig. 419—Bilateral abducens palsy due to increased intracranial pressure. (From *Crimmer Neurology Course*, of Charles C. Thomas, Publisher, Springfield, Ill.)

In summary, therefore, any patient, either a child or an adult, who shows progressive development of neurological symptoms, should be regarded as a tumor suspect and if in addition signs of increased intracranial pressure make their appearance the diagnosis is almost certain, and treatment should not be delayed.

**Types**—Gliomas form the largest single group of primary brain tumors and total about 41 per cent of these. They have been classified by Bailey according to their predominant cell type and their malignancy. Generally depends on the embryonic character of the cells which predominate in them. Glioblastoma multiforme (Fig. 420) forms 30.2 per cent of the gliomas and is a very malignant tumor which usually causes death within a period of twelve months. The onset and course are rapid in this type of tumor. It

the nervous system to another by way of the subarachnoid space. Consequently, tumors involving the nervous system may be single or multiple. Pathological studies of these tumors in a large series of cases have been of great value. This is particularly important from the standpoint of prognosis because statistical studies have yielded information from which the life expectancy of patients with different types of tumors can be determined. Pathological classification has also been of value in affording data by means of which the type of tumor can sometimes be determined because of its location, or of the age of the patient, or the signs manifested, or the duration of symptoms.

### Intracranial Tumors

**General Symptomatology**—Brain tumors, being space occupying masses which gradually increase in size, usually have a clinical history of slow, gradual progression of signs. Not infrequently, however, the patient will first become aware of his illness because of the sudden development of symptoms. This may be due to vascular lesions, occurring in connection with tumor, or to the location and nature of the tumor. Consequently the history of a slow, progressive illness, manifested by the signs of a single lesion, renders the patient a tumor suspect. It must be borne in mind that brain tumors occur frequently in children, in whom they are usually located in the posterior fossa and consequently increase intracranial pressure rapidly. The increase in size of the tumor, growing within the rigid, bony skull, will increase intracranial pressure and cause characteristic symptoms. This is particularly true of posterior fossa lesions because the posterior fossa is a small chamber bounded by bone and tentorium, and also because pressure within it is easily transmitted to the channel by which cerebrospinal fluid escapes from the ventricular system.

The signs of increased intracranial pressure are headache, vomiting, and papilledema. The headache is not usually of localizing value, although in tumors of the posterior fossa it is usually located in the occipital region and down the neck. The headache at the onset is often intermittent and occurs most frequently in the morning. It increases in severity and finally may become continuous. It is usually made worse by activity which will increase intracranial pressure such as stooping over, coughing, or straining at stool. It is often described as a bursting sensation. Vomiting often accompanies the headache. It is usually stated that the vomiting associated with increased intracranial pressure is of a projectile type, and that it occurs suddenly and forcibly and without nausea. While this type of vomiting may occur especially in children with cerebellar tumors, the vomiting is usually associated with some nausea. Papilledema is due to interference with the venous return of blood from the eyes because of the increase in intracranial pressure. The optic discs become edematous, their margins are blurred, the veins become tortuous and dilated, the optic cups are filled in and exudate obscures the vessels and elevates the surface of the discs. Early in its course it may be associated with very little change in visual acuity. Papilledema unless relieved goes on to secondary optic atrophy and when this is complete, blindness results. It has already been stated that increased intracranial pressure fre-

quently leads to paralysis of one or both sixth nerves, with consequent paralysis of external rotation of the eye or eyes and convergent strabismus (Fig. 419)

Convulsions beginning in adult life must be regarded as due to structural change in the central nervous system unless proved otherwise. These convulsions may be general but are usually focal and are referred to under the heading of *Focal Symptomatology*. Mental disturbances occur in brain tumors, but it is surprising how indistinct a relationship there is between the location of the tumor and the type or degree of mental disturbance. These symptoms occur more prominently in frontal and temporal lobe lesions in tumors of the corpus callosum, and also in cerebellar tumors, in which they frequently do not appear until after the removal of the tumor or the release of the increased intracranial pressure. The mental symptoms are usually those of intellectual deterioration. There are some confusion, impairment of memory, inattentiveness, loss of initiative and dullness, and late cases may go on to stupor.



Fig. 419.—Bilateral abducens palsy due to increased intracranial pressure. (From Grinker *Neurology*, Copyright of Charles C Thomas Publisher, Springfield, Ill.)

In summary therefore any patient, either a child or an adult who shows progressive development of neurological symptoms should be regarded as a tumor suspect, and if, in addition, signs of increased intracranial pressure make their appearance the diagnosis is almost certain and treatment should not be delayed.

**Types**—Gliomas form the largest single group of primary brain tumors and total about 41 per cent of these. They have been classified by Bailey according to their predominant cell type and their malignancy generally depends on the embryonic character of the cells which predominate in them. Glioblastoma multiforme (Fig. 420) forms 70.2 per cent of the gliomas and is a very malignant tumor which usually causes death within a period of twelve months. The onset and course are rapid in this type of tumor. It

the nervous system to another by way of the subarachnoid space. Consequently, tumors involving the nervous system may be single or multiple. Pathological studies of these tumors in a large series of cases have been of great value. This is particularly important from the standpoint of prognosis because statistical studies have yielded information from which the life expectancy of patients with different types of tumors can be determined. Pathological classification has also been of value in affording data by means of which the type of tumor can sometimes be determined because of its location, or of the age of the patient or the signs manifested, or the duration of symptoms.

### Intracranial Tumors

**General Symptomatology**—Brain tumors, being space occupying masses which gradually increase in size, usually have a clinical history of slow, gradual progression of signs. Not infrequently, however, the patient will first become aware of his illness because of the sudden development of symptoms. This may be due to vascular lesions, occurring in connection with tumor, or to the location and nature of the tumor. Consequently the history of a slow, progressive illness, manifested by the signs of a single lesion renders the patient a tumor suspect. It must be borne in mind that brain tumors occur frequently in children, in whom they are usually located in the posterior fossa and consequently increase intracranial pressure rapidly. The increase in size of the tumor, growing within the rigid, bony skull, will increase intracranial pressure and cause characteristic symptoms. This is particularly true of posterior fossa lesions because the posterior fossa is a small chamber bounded by bone and tentorium, and also because pressure within it is easily transmitted to the channel by which cerebrospinal fluid escapes from the ventricular system.

The signs of increased intracranial pressure are headache, vomiting, and papilledema. The headache is not usually of localizing value, although in tumors of the posterior fossa it is usually located in the occipital region and down the neck. The headache at the onset is often intermittent and occurs most frequently in the morning. It increases in severity and finally may become continuous. It is usually made worse by activity which will increase intracranial pressure, such as stooping over, coughing, or straining at stool. It is often described as a bursting sensation. Vomiting often accompanies the headache. It is usually stated that the vomiting associated with increased intracranial pressure is of a projectile type, and that it occurs suddenly and forcibly and without nausea. While this type of vomiting may occur especially in children with cerebellar tumors, the vomiting is usually associated with some nausea. Papilledema is due to interference with the venous return of blood from the eye because of the increase in intracranial pressure. The optic discs become edematous, their margins are blurred, the veins become tortuous and dilated, the optic cups are filled in and exudate obscures the vessels and elevates the surface of the discs. Early in its course it may be associated with very little change in visual acuity. Papilledema unless relieved goes on to secondary optic atrophy and when this is complete blindness results. It has already been stated that increased intracranial pressure fre-

of adults and the cerebellum of children. These tumors are often cystic, grow slowly and are compatible with an average survival of over six years. They are more circumscribed than other gliomas. Tumor tissue itself may form but a small nodule in the wall of a cyst. Sometimes areas of calcification occur and these can be seen on x-ray examination. Astroblastomas form 5.1 per cent of the group and occur in the cerebral hemispheres of adults. They have an average life expectancy of thirty seven months from the onset of symptoms. Cysts are not common in this tumor but do occur. The cells in it have sucler feet attached to blood vessels and there is a marked proliferation in the adventitia of the blood vessels. Oligodendrogliomas form 4 per cent of the group and are solid tumors which occur in the cerebral hemispheres of adults. Usually there is some calcification in these tumors so that they also may be detected on x-ray examination. They are slow growing and compatible with many years of life. Spongioblastomas form 4.7 per cent of the group and occur along the cerebral axis in young adults or adolescents. They are frequent in the optic chiasm and brain stem. Their location makes them difficult to approach. Ependymomas (fig. 422) form 3.7 per cent of the group and occur chiefly in children and about the ventricles. They are slow growing, but owing to their location, they are not compatible with long life. Calcification frequently appears within the tumor. Pineal tissue is derived from neuroepithelium and pinealomas form about 2 per cent of this group of tumors. They may occur at any age but are most common in young males in whom they cause precocious puberty and paralysis of upward conjugate movements of the eyes in addition to signs of compression and of increased intracranial pressure. Ganglioneuromas form only about 0.4 per cent of this group and are made up of glia cells in all stages of development, and neurocytes, many of which are adult types with Nissl bodies. These ganglion cells may be multinucleated. Neuroepitheliomas are rare tumors in the brain but occur in the retina and spinal cord.

Meningiomas constitute about 13 per cent of intracranial tumors. They are also called dural endotheliomas and meningeal fibroblastomas. They are composed of specialized connective tissue cells resembling those which form the arachnoidal villi, and it is probable that they arise from these structures. They grow slowly, are encapsulated and excellent results follow their removal. They arise most commonly along the anterior half of the superior longitudinal sinus along the course of the middle meningeal vessels in the olfactory grooves and in the regions of the lesser wing of the sphenoid and the tuberculum sellae. They may be large and lobulated or flat. The capsule usually is very vascular and this makes removal of the tumor difficult. In addition the scalp and overlying bones are usually vascular as well. The cells are often arranged in whorls which may become hyalinized and calcified and are then referred to as psammoma bodies. They may cause erosion and proliferation of the skull. The increased vascularity, the calcification and the changes in the bones of the skull may all be apparent on x-ray examination and thus indicate the type of tumor that exists. This tumor, which is of mesodermal origin, does not invade the brain tissue but compresses it.

occurs almost always in the cerebral hemispheres of adults, and infiltrates widely. Within it there may be areas of hemorrhage, degeneration and cyst formation. It is made up of cells of many sizes and shapes and many mitotic figures and multinucleated cells can be seen. There is no single predominating cell. The blood vessels are abnormal, and hemorrhages and thromboses may occur. This type of tumor may show few symptoms even though quite large and the onset of those symptoms may be sudden. Medulloblastoma (Fig 421) forms 12.6 per cent of the group and usually occurs in the cerebellum of children.



Fig 420 — Glioblastoma multiforme of the right parietal lobe

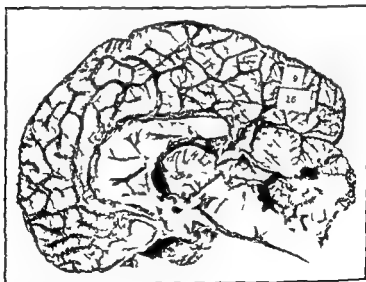


Fig 421 — Medulloblastoma of the cerebellum

This tumor metastasizes in the subarachnoid space. Because of its location it bulges into the fourth ventricle and usually causes hydrocephalus. Cerebellar symptoms may not be severe and may be limited to trunkal ataxia. The early manifestations of the tumor may be regarded as due to a disturbance of the gastrointestinal tract and their true nature may not be appreciated for some time. Astrocytomas form 37 per cent of the group and occur in the cerebrum.



their dural envelope to extend into the intracranial cavity. Hypophyseal duct tumors (Fig. 424) are also called craniopharyngiomas, adamantinomas and tumors of Rathke's pouch, and form 4.5 per cent of all intracranial tumors. They occur particularly in children and arise from squamous epithelial rests within the hypophysis. They are suprasellar, usually cystic and frequently become calcified, so that they can be seen on x-ray examination in their typical location. They may also be found in adults. They are composed of epithelial cells of ectodermal origin.



Fig. 424—Erosion and enlargement of the sella turcica caused by pituitary adenoma.

Blood vessel tumors form about 20 per cent of all intracranial tumors. They are composed of two types, the angiomas which are malformations and have been referred to on page 1111 and the hemangioblastomas which are true neoplasms. Angiomas are frequently associated with vascular abnormalities elsewhere such as in the face or scalp. They are made up of tangles of tortuous vessels the walls of which are pathological. They occur most commonly in the cerebrum although the cerebellum and brain stem may be involved. The vessel walls are sometimes calcified. Sometimes a bruit can be heard by the patient and by the examiner on auscultation of the head. Hemangioblastomas occur almost exclusively in the cerebellum and are usually cystic. They are sometimes associated with angiomas of the retina and cysts of the pancreas and kidney and the condition is then known as Landau's disease. This disease is familial and on x-ray examination calcified rings may be seen

Perineurial fibroblastomas, as the name indicates, arise from the sheaths of nerve roots or nerves. They occur particularly on the auditory nerve, and in that location form about 90 per cent of intracranial tumors. They produce the symptoms characteristic of involvement of the cerebellopontine angle. They usually occur in middle aged adults and grow slowly. They are usually unilateral and occasionally bilateral, but in the latter case they are more likely to be lesions of von Recklinghausen's disease which is a different entity.

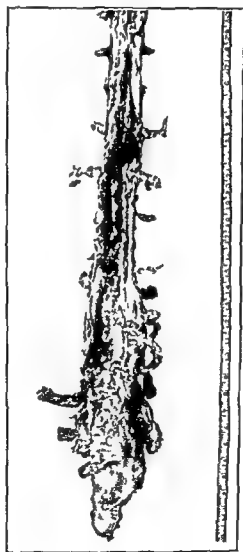


Fig. 4 — An ependymoma of the cauda equina

They compress the structures in the angle in which they lie and produce characteristic symptoms (see page 1016). They are composed of elongated spindle shaped cells with ovoid nuclei.

The common pituitary tumors are adenomas which form about 17.0 per cent of intracranial tumors. They occur primarily in young adults and they produce characteristic endocrine disturbances which are described in Chapter XIV. As they grow they erode the sella turcica (Fig. 423) and break through

body. The extent of this paralysis will depend upon the location and the size of the lesion. It has been explained how the leg is represented uppermost in the motor cortex and the face lowermost. In paralysis associated with a frontal lobe tumor the arm is frequently involved most. The facial paralysis which may occur is of the central or supranuclear type with involvement of the corner of the mouth and not of the muscles of the forehead. Mental symptoms may be present or may be absent and it is surprising what little mental disturbance may follow complete removal of the frontal lobe anterior to the motor cortex. If there is no constant weakness or paralysis there may be a transitory impairment of function on the opposite side of the body following Jacksonian epileptic attacks. In cases with hemiplegia the gait is that typical of the condition. The knee is held more or less stiffly extended and the foot somewhat plantar flexed so that in walking the patient has to circumduct the entire leg to lift it from the ground. Even with this movement the toes usually scrape along the ground. If the involvement is in the dominant hemisphere and near the Sylvian fissure aphasia usually of the motor type, will occur. Tumors on the inferior surface of the frontal lobe in the olfactory groove cause anosmia.

*Temporal Lobe.* In temporal lobe lesions also Jacksonian convulsions may be present and these have been described. Otherwise the tumor may cause but few focal symptoms. Frequently mental disturbances and confusion occur. The visual or optic radiations are usually involved and this leads to a hemianopia or quadrantic loss of vision in the opposite visual field. When the tumor occurs in the dominant hemisphere there is usually aphasia involving all spheres of speech. This is particularly true in left-sided tumors in right-handed individuals but not uncommonly right-sided tumors in left-handed individuals will not cause aphasia. Visual hallucinations occur also in temporal lobe tumors whereas in occipital lobe tumors visual phenomena of a positive nature are usually limited to flashes of light. Dreamy states and the typical uncinate fits described on page 1009 occur. Extension of the tumor may cause contralateral paralysis.

*Parietal Lobe.* Tumors of the parietal lobe give rise to sensory disturbances chiefly of the type of astereognosis and inability to discriminate between the texture, size and shape of different objects. The Jacksonian attacks arising from lesions in this lobe usually begin with sensory manifestations on the opposite side of the body. Tumors of the parietal lobe may produce defects in the visual fields of the opposite side and also when located in the dominant hemisphere may lead to some aphasic disturbances.

*Occipital Lobe.* The most constant sign in occipital lobe tumors is a contralateral homonymous hemianopia with sparing of macular vision (page 1000). In addition subjective visual phenomena may be present and may occur as part of a Jacksonian epileptic attack or not. They consist of flashes of light or colors or stars in the opposite visual field. Frequently also there is an aphasic disorder if the tumor extends far forward and this consists typically of a defect in reading and writing with minimal disturbances in other types of speech function.

within the retina due to changes in the lesions there. Papillomas of the choroid plexus form 0.5 per cent of intracranial tumors and arise from the choroid plexus in the fourth ventricle most frequently. They have also been found in other parts of the ventricular system and they are most common in children. They are formed of vascular cores covered by cuboidal epithelium. The only manifestation may be that they periodically block the foramina in the ventricular cavities and cause headache which may be relieved by alteration in the position of the head. They respond well to x-ray treatment.

Metastatic tumors form about 50 per cent of intracranial neoplasms. The order of frequency is carcinoma, sarcoma, hypernephroma. The most common source of carcinoma is the lungs or bronchi and these give rise to about 30 per



Fig. 44.—Calcification in the wall of a craniopharyngeal pouch cyst lying above the sella turcica.

cent of the intracranial metastases. The primary source may also be in the breast, stomach, pancreas or prostate. They are usually multiple and undergo degeneration and cyst formation. They resemble the primary tumor and cause marked reaction in the brain. Sometimes the carcinoma cells can be found in the spinal fluid. Apart from the formation of metastases, carcinoma can involve the intracranial structures by direct extension from the nasopharynx.

**Focal Symptomatology—Frontal Lobe.** Lesions of the frontal lobe commonly cause Jacksonian epileptic attacks and the character of these has been described on page 1009. In addition because of impairment of motor pathways, there is usually a weakness or paralysis on the opposite side of the

**body** The extent of this paralysis will depend upon the location and the size of the lesion. It has been explained how the leg is represented uppermost in the motor cortex and the face lowermost. In paralysis associated with a frontal lobe tumor the arm is frequently involved most. The facial paralysis which may occur is of the central or supranuclear type with involvement of the corner of the mouth and not of the muscles of the forehead. Mental symptoms may be present or may be absent and it is surprising what little mental disturbance may follow complete removal of the frontal lobe anterior to the motor cortex. If there is no constant weakness or paralysis, there may be a transitory impairment of function on the opposite side of the body following Jacksonian epileptic attacks. In cases with hemiplegia the gait is that typical of the condition. The knee is held more or less stiffly extended and the foot somewhat plantar flexed so that in walking the patient has to circumduct the entire leg to lift it from the ground even with this movement the toes usually scrape along the ground. If the involvement is in the dominant hemisphere and near the Sylvian fissure aphasia usually of the motor type will occur. Tumors on the inferior surface of the frontal lobe in the olfactory groove cause anosmia.

**Temporal Lobe** In temporal lobe lesions also Jacksonian convulsions may be present and these have been described. Otherwise the tumor may cause but few focal symptoms. Frequently mental disturbances and confusion occur. The visual or optic radiations are usually involved and this leads to a hemianopic or quadrant loss of vision in the opposite visual field. When the tumor occurs in the dominant hemisphere there is usually aphasia involving all spheres of speech. This is particularly true in left sided tumors in right handed individuals but not uncommonly right sided tumors in left handed individuals will not cause aphasia. Visual hallucinations occur also in temporal lobe tumors whereas in occipital lobe tumors visual phenomena of a positive nature are usually limited to flashes of light. Dreamy states and the typical uncinate fits described on page 1009 occur. Extension of the tumor may cause contralateral paralysis.

**Parietal Lobe** Tumors of the parietal lobe give rise to sensory disturbances chiefly of the type of astereognosis and inability to discriminate between the texture size and shape of different objects. The Jacksonian attacks arising from lesions in this lobe usually begin with sensory manifestations on the opposite side of the body. Tumors of the parietal lobe may produce defects in the visual fields of the opposite side and also when located in the dominant hemisphere may lead to some aphasic disturbances.

**Occipital Lobe** The most constant sign in occipital lobe tumors is a contralateral homonymous hemianopia with sparing of macular vision (page 1000). In addition subjective visual phenomena may be present and may occur as part of a Jacksonian epileptic attack or not. They consist of flashes of light or colors or stars in the opposite visual field. Frequently also there is an aphasic disorder if the tumor extends far forward and this consists typically of a defect in reading and writing with minimal disturbances in other types of speech function.

*The Third Ventricle* Signs referable to the third ventricle may be caused by tumors within the ventricle, by invasion from tumors about the ventricle, or by compression, as in pineal tumors. Intermittent headache is frequently a common symptom and may sometimes be relieved by changing the position of the head, or by a sudden movement of it. This is explained on the basis that the tumor within the third ventricle intermittently blocks the escape of cerebrospinal fluid, and causes temporary increase of pressure within the proximal part of the ventricular system. Commonly also tumors in this location will produce somnolence of a characteristic type which resembles that of narcoleptic attacks. The patient may fall asleep while in the midst of any occupation or while at rest. The sleep is apparently a normal one and the patient can be aroused from it. Sometimes also there are disturbances in body temperature, and hyperthermia is frequently a serious complication of operations in this region. There is a close physiological relationship between the pituitary gland and the floor of the third ventricle, in the region of the tuber cinereum, so that endocrine and metabolic disturbances of a similar character are produced by lesions in these two regions. It has already been stated that in this part of the brain the head centers for the sympathetic and parasympathetic nervous systems are located, and Penfield has described disturbances of these functions occurring as epileptic phenomena in a case of tumor of the third ventricle. These so called diencephalic autonomic epileptic attacks were manifested by changes in peripheral circulation and in sweating.

Tumors in the region of the optic chiasm produce a bitemporal hemianopsia which was described on page 998. Gliomas directly involving the chiasm may produce irregular defects in the visual field and also primary optic atrophy. By extension forward, they may involve the nerves to the external ocular muscles and produce paralysis of these with diplopia and strabismus. Sometimes they produce dilatation of the optic foramina. Tumors of the pineal gland (Fig. 425 and Figs. 367 and 368) may show signs of involvement of the third ventricle, and are frequently associated with precocious puberty in young boys. They also cause increase in intracranial pressure and by involvement of the roof of the midbrain paralysis of upward conjugate deviation of the eyes and sometimes other ocular disturbances. Tumors of the thalamus may produce a typical syndrome consisting of a partial loss of sensibility on the opposite side of the body, pains and paraesthesiae on the opposite side of the body, and an exaggerated response to sensory stimulation in the involved area. Sometimes partial hemiplegia and abnormal movements on the opposite side of the body occur. The sensory disturbances are more typical than the motor ones and sensory stimulation of the skin causes disagreeable and painful sensation.

*Tumors of the Pons and Medulla* : The symptoms in tumors of these regions will depend upon the cranial nerve nuclei and the projection pathways that are involved. The fifth sixth seventh eighth ninth tenth and twelfth cranial nerves may all be involved and usually the disability is bilateral. Various combinations may be picked out or the involvement may be entirely on one side. The pyramidal and sensory pathways in the brain stem may

also be affected. If the tumor is unilateral the cranial nerve paralysis will be homolateral and involvement of the pyramidal tract will lead to a hemiplegia on the contralateral side. Tumors arising in the brain stem show signs of increased intracranial pressure only late, but tumors within the fourth ventricle, on the other hand, produce increased intracranial pressure very early. Cerebellar symptoms commonly occur from involvement of the cerebellar peduncles.

**Cerebellum.** Signs of a lesion in one cerebellar hemisphere have been described already on page 989. When the lesion is in the midline in the vermis the difficulties are mainly in gait and station and the patient tends to stagger and sway as he walks. The head may be held stiffly and the neck may be rigid. Other cerebellar signs may be present, such as those that occur in hemispherical lesions but they are frequently absent. These tumors early produce an increase in intracranial pressure and signs of this are added to the focal symptomatology. From compression various cranial nerves may be paralyzed but the tracts in the brain stem are not usually involved until very late in the course of the disease.

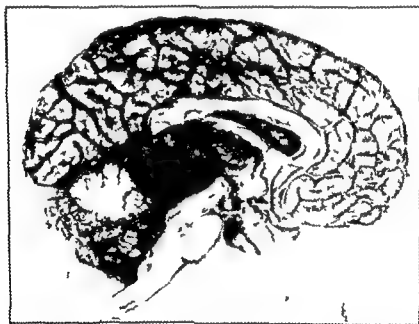


Fig. 1028. — A large posterior fossa tumor.

Occasionally homolateral hemiplegia rather than contralateral hemiplegia may occur in brain tumors because of compression of the opposite cerebral peduncle against the free edge of the tentorium.

The pathological findings that may be present on x-ray examination in cases of intracranial tumor have already been discussed (page 1028). Erosion, calcification, bone proliferation and increase in vascularity may all serve as localizing signs. In addition the pineal gland (normal calcification in the pineal gland) may be displaced and convolutional markings in the skull may

be evidence of increased intracranial pressure. The various distortions and displacements of the ventricles which may be found when they are filled with air and then x-rayed have been referred to. Information of extreme localizing value may be given by this means. Other necessary examinations, such as the labyrinthine tests may also yield important information.

Electroencephalography, and its value in the study and localization of brain tumors is described in the section dealing with epilepsy (page 1153).

**Treatment**—The treatment of brain tumors should be directed by a neurosurgeon. Removal of the tumor is often possible and in some cases may be complete. The prognosis, while always serious, is often compatible with many years of active life. In some cases x-ray treatment is a valuable adjunct to surgical treatment.

### Intraspinal Tumors

Intraspinal tumors may be extramedullary or intramedullary. The extramedullary tumors are by far the more common and can be further subdivided into intradural and extradural. Tumors of the vertebral column, such as sarcoma, chondroma and metastatic carcinoma, cause neurological manifestations through compression of the spinal cord. The great majority of extramedullary tumors are meningeal fibroblastomas and perineurial fibroblastomas whereas the intramedullary tumors are chiefly gliomas.

**Symptoms**—The onset of symptoms in extramedullary tumors is usually slow and may extend over several months or even a few years. Usually the first manifestation is pain and this is due to irritation of the posterior nerve roots. Consequently it is located in the distribution of the roots and it may be unilateral or bilateral. It is commonly described as a feeling of constriction or of a girdle and it is made worse by coughing, or straining at stool, or other measures which tend to increase intraspinal pressure. Local pain and tenderness over the vertebral column also occur and these are particularly evident in tumors of the vertebral column itself. As the tumor compresses the spinal cord it causes symptoms referable to this. The first manifestations are those of a slowly developing spastic paralysis and the spasticity is usually a prominent feature of this. The paralysis is of the upper motor neurone type and its distribution will depend upon whether one or both sides of the cord are compressed and at what level it is compressed. Sensory impairment also occurs and this likewise is a level loss. Frequently the sphincters are involved so that retention or incontinence occurs. Bed sores and bladder infections are frequent complications. If the anterior roots are involved there will be atrophy at the level of the lesion in its segmental distribution. Flexor spasms of the legs are sometimes very troublesome to the patient especially at night. If the tumor is on the posterolateral surface of the cord a Brown Sequard type of paralysis (see page 1018) is most likely to occur. If it is in the midline the pathological manifestations will be symmetrical from the start. In cases of tumors on the anterior surface of the cord such as chondroma pain is not a prominent symptom and segmental atrophy and fibrillation are likely to occur.



Intramedullary tumors are much less common than the extramedullary type but differentiation clinically is often impossible and always difficult. In these cases pain is often escaped involvement and sometimes at the level of the lesion there is a dissociation of sensation such as occurs in myelomelia. Root pains are not common although stiffness and pain in the back frequently occur. In tumors of the cord the paraplegia may be in flexion or extension (see page 1018).

The diagnosis of the level of an intraspinal lesion may be difficult and may depend almost entirely on an accurate interpretation of the sensory loss. Examination of sensation in such cases must be a painstaking operation which requires the fullest concentration on the part of both physician and patient. Charts of the segmental distribution of the spinal cord are shown on page 947 and it is by means of excluding the symptoms in terms of the anatomical facts that accurate topographical diagnosis is made.

The use of roentgenograms and examination of the cerebrospinal fluid are of great value in the diagnosis of cord lesions. X-ray examination will show the presence of metastatic growths when they occur in the vertebral column and sometimes in intraspinal lesions. Erosions of the bone and widening of the interpedicular spaces may be seen. In addition when it is necessary lipiodol may be injected and in the presence of a block will outline the level of the lesion. The principles of the Queckenstedt test have already been described (page 1027) and by means of this block in the cerebrospinal fluid circulation can be shown. In cases of block the fluid distal to the block contains an increase of protein. In long standing cases of complete block the fluid in addition is yellow or xanthochromic and will coagulate spontaneously on standing (Froin's syndrome).

In lesions of the cauda equina pain and paresthesia are common symptoms. The pain will often be in the distribution of the sciatic nerve and may be regarded as sciatica for some time. With such tumors weakness and paralysis are of the lower motor neurone type and sensory loss will conform to the segmental distribution of the nerve roots involved. Bladder disturbances generally occur and may begin early in the course of the illness.

**Prognosis**—The prognosis in extramedullary tumors arising from the dura is very good that in metastatic lesions of the vertebral column is of course bad. Sometimes an intramedullary tumor may be partially removed.

**Treatment**—The treatment of cord tumors should be under the direction of a neurosurgeon. The results are so gratifying in many cases that treatment should be carried out early and before paralysis becomes complete. This early treatment is essential in order to prevent irreparable damage to the spinal cord and cord tumor cases should be regarded as emergencies.

### Neurofibromatosis

**Synonym**—Von Recklinghausen's disease

**Definition**—This disease is often hereditary and sometimes occurs in families. It is probably related to the familial type of hypertrophic interstitial neuritis. It is characterized by areas of cutaneous pigmentation multiple sessile or pedunculated soft or firm masses in the skin subcutaneous

be evidence of increased intracranial pressure. The various distortions and displacements of the ventricles, which may be found when they are filled with air and then x-rayed, have been referred to. Information of extreme localizing value may be given by this means. Other accessory examinations such as the labyrinthine tests may also yield important information.

Electroencephalography and its value in the study and localization of brain tumors is described in the section dealing with epilepsy (page 1113).

**Treatment**—The treatment of brain tumors should be directed by a neurosurgeon. Removal of the tumor is often possible, and in some cases may be complete. The prognosis while always serious is often compatible with many years of active life. In some cases, x-ray treatment is a valuable adjunct to surgical treatment.

### Intraspinal Tumors

Intraspinal tumors may be extramedullary or intramedullary. The extramedullary tumors are by far the more common and can be further subdivided into intradural and extradural. Tumors of the vertebral column, such as sarcoma, chondroma and metastatic carcinoma, cause neurological manifestations through compression of the spinal cord. The great majority of extramedullary tumors are meningeal fibroblastomas and perineurial fibroblastomas, whereas the intramedullary tumors are chiefly gliomas.

**Symptoms**—The onset of symptoms in extramedullary tumors is usually slow and may extend over several months or even a few years. Usually the first manifestation is pain and this is due to irritation of the posterior nerve roots. Consequently it is located in the distribution of the roots and it may be unilateral or bilateral. It is commonly described as a feeling of constriction or of a girdle and it is made worse by coughing, or straining at stool, or other measures which tend to increase intraspinal pressure. Local pain and tenderness over the vertebral column also occur and these are particularly evident in tumors of the vertebral column itself. As the tumor compresses the spinal cord it causes symptoms referable to this. The first manifestations are those of a slowly developing spastic paralysis and the spasticity is usually a prominent feature of this. The paralysis is of the upper motor neurone type and its distribution will depend upon whether one or both sides of the cord are compressed and at what level it is compressed. Sensory impairment also occurs and this likewise is a level loss. Frequently the sphincters are involved so that retention or incontinence occurs. Bed sores and bladder infections are frequent complications. If the anterior roots are involved there will be atrophy at the level of the lesion in its segmental distribution. Flexor spasms of the legs are sometimes very troublesome to the patient especially at night. If the tumor is on the posterolateral surface of the cord a Brown Sequard type of paralysis (see page 1018) is most likely to occur. If it is in the midline the pathological manifestations will be symmetrical from the start. In cases of tumors on the anterior surface of the cord such as chondromas pain is not a prominent symptom and segmental atrophy and fibrillation are likely to occur.

involves the fibers in the commissure. In this disease it is sometimes found that there is a dissociation of these two types of sensibility and frequently temperature or pain sensibility will be lost separately at different levels. Because of the impairment of thermal sensibility, the patients may accidentally burn their fingers without being aware of it. Occasionally, spontaneous pain will be complained of in the segmental distribution of the lesion. As the lesion extends up and down the cord the area of loss of pain and temperature sensibility becomes widened but rarely extends below the tenth dorsal segment. Extension into the upper cervical cord will involve the fifth nerve and produce the same type of sensory loss in the face. As the lesion extends transversely in the cord, it involves other structures. Extension to the anterior grey horn will produce *weakness and wasting of the muscles* in the segmental distribution usually in the small muscles of the hand. This may lead to a "clawhand" deformity such as occurs in ulnar nerve paralysis. The symptoms may be bilateral from the beginning or one side may be affected before the other. As the disease progresses there is sometimes degeneration of the pyramidal tracts with signs of an upper neurone type of paralysis below the lesion. From extension to the medulla weakness of the soft palate, pharynx and vocal cords may result, and sometimes other cranial nerves will also be involved. There are frequently fibrillary twitchings to be seen in the distribution of the peripheral motor cells that are involved. From atrophy and weakness of the muscles of the back, scoliosis frequently occurs. Involvement of the lateral horns of grey matter produces vasomotor disturbances which consist of edema of the hands, excessive sweating and sometimes Horner's syndrome. Trophic disturbances such as Charcot's joints, atrophy of bone ulcerations and whitlows occur. Other congenital anomalies may be associated with this condition, such as cervical rib. Occasionally the course may be sudden, but usually it is very slowly progressive and may come to a standstill for some years. If the condition is posttraumatic and associated with adhesive arachnoiditis there may be signs of partial or complete block with the Queckenstedt test.

**Pathological Anatomy**—The cord is enlarged and the arachnoid may be thickened. Within the cord there are cavities which extend a variable distance both longitudinally and transversely. The process begins most frequently at the base of one posterior horn or in the center of the cord near the central canal. Surrounding the cavity there is an area of gliosis.

**Prognosis**—The condition is chronic and progresses slowly. Remissions may occur so that it is stationary for years but there may be at any time a sudden intensification.

**Treatment**—X ray treatment over the affected region of the spinal cord may bring about considerable relief. Occasionally surgical treatment by decompression and incision of the cyst is necessary.

### Alzheimer's Disease

**Synonym**—Presenile dementia

**Definition**—Alzheimer's disease is a slow progressive dementia with focal symptoms such as aphasia and apraxia which begins between the ages of forty and sixty years. The dementia is progressive and leads to loss of

nodules and enlargements of the peripheral nerves. Lesions may occur in the peripheral or central nervous system or in the meninges. Penfield and Young\* have described the essential pathological changes as hyperplastic reactions of cells peculiar to the tissues involved and superimposed on, or subsequent to, this the appearance of neoplastic growth of these cells. Changes may occur in the bones and also deformities like those of elephantiasis may occur in the legs. The neurofibromatosis may involve the cranial nerves, or the peripheral nerve roots or peripheral nerves and the symptoms will depend on the size and location of the lesions. Frequently multiple cranial or peripheral nerve palsies occur and in addition there may be signs of focal brain or cord lesions. Biopsy of an accessible lesion will indicate the pathological nature of the disease.

## DEGENERATIVE DISEASES AND DISEASES OF UNKNOWN CAUSE

### Syringomyelia and Syringobulbia

**Definition**—A chronic disease characterized by formation of cavities in the cord, and sometimes extending into the medulla, and manifested clinically by segmental signs usually of a sensory nature and frequently by involvement of tracts in the cord.

**Etiology**—The exact etiology is unknown. The condition is believed to be due to a proliferation of glia in the region of the central canal of the cord and the formation of cavities by degeneration of these proliferated areas. The gliosis and cavity formation are usually in the region of the central canal, but may extend into the white matter also. It extends up and down the cord for a variable distance. Sometimes other members of the family may show evidence of developmental abnormalities. Cavities in the cord may also follow trauma when this is associated with adhesive arachnoiditis and interference with the vascular supply to the cord. Degeneration and cyst formation follow this vascular complication and are usually situated in the posterior horn of grey matter.

**Symptoms**—The condition begins in the second or third decade of life and males are more often affected than females. The usual location is in the lower cervical and upper thoracic cord. The most characteristic clinical findings are those relating to the central position of the lesion in the cord. It has been described how sensory fibers carrying pain and temperature sensibility enter the cord through the posterior nerve roots. They terminate in the posterior grey horns, and new fibers convey the sensation to the opposite side of the cord, through the anterior commissure ventral to the central canal. A lesion placed centrally in the cord in the region of the central canal will therefore first interfere with transmission of impulses along these crossing fibers and will produce impairment of sensibility in the segmental distribution from which the fibers have been derived. Furthermore the types of sensibility impaired will be those of pain and temperature. The common distribution of the impairment is over the ulnar border of the hand forearm and arm and across the upper part of the chest and back. The sensory loss will be present on one side, if the lesion is in the posterior grey horn and on both sides if it

present. The characteristic sensory disturbance is a loss of muscle or position sensibility and vibration sensibility, and ataxia results from this. The mechanism of the ataxia is similar to that described under the heading of *Tabes Dorsalis*, but in posterolateral sclerosis the ataxic manifestations are complicated by the signs of pyramidal tract involvement. Sometimes also other forms of sensation are impaired and analgesia and hypesthesia may be present in a 'glove' or 'stocking' distribution. Motor manifestations begin gradually with fatigue of the legs, dragging of the feet and finally a weakness which is progressive. The knee jerks and ankle jerks may be increased or absent depending upon the relative degree of motor or sensory involvement. In the same way some cases manifest rigidity and some flaccidity. The plantar responses are usually extensor. The symptoms are always more prominent in the legs and the arms may manifest only paraesthesiae. The sphincter control frequently becomes impaired and trophic changes sometimes occur. In addition to the symptoms of subacute combined degeneration the symptoms of pernicious anemia are usually present in varying degrees. Absence of free hydrochloric acid in the stomach is a constant finding in pernicious anemia and the same is true of subacute combined degeneration even when this latter disease is associated with a hypochromic rather than a pernicious anemia. Not infrequently the involvement of the nervous system occurs before the signs of anemia are obvious and the diagnosis of pernicious anemia may be made first by the neurologist who sees the patient. Mental changes may occur, and may be of a confusional or an affective type. Not infrequently symptoms of neuritis are combined with those of posterolateral sclerosis or completely overshadow them.

**Pathological Anatomy**—There is extensive softening in the cord with large and small foci of destruction. The neuroglia are also affected in this destructive process. Lipoid products of degeneration in the focus are removed by compound granular corpuscles. There is a feeble connective tissue response and in the areas of healthy tissue there is some proliferation of neuroglia. The blood vessels are thickened and there may be secondary inflammatory changes going on about them. Areas of perivascular necrosis and of chromatolysis occur also in the brain.

**Prognosis**—With intensive treatment of the pernicious anemia it is possible to bring about improvement and to prevent progression in early cases. When objective manifestations are marked little improvement is to be expected.

**Treatment**—The treatment is that of pernicious anemia. Intensive treatment of the pernicious anemia must be carried out (see page 545) with the administration of the equivalent of at least 200 grms of liver extract a week. Bed rest is necessary for the first few months of treatment and physiotherapy may be of value.

### Lead Encephalopathy

**Etiology**—Lead can reach the body from many sources. It usually gains access through the gastrointestinal tract and may be ingested in food or drinking water or inhaled from face powder or snuff. In addition children frequently ingest it by chewing painted articles. Lead may be stored in the bones and liver, kidney and nervous tissue for many years without producing

memory, intellectual deterioration, and personality changes. Tremors and convulsions may occur. The speech becomes slowed, dysarthric, and unintelligible.

**Pathological Anatomy**—There are degeneration of the cortical ganglion cells and the presence of senile plaques in the cortex. The brain is shrunken and the pia mater usually thickened. There is degeneration of the neurofibrils some of which break up and others agglutinate to form distorted, tangled strands.

### Senile Dementia

This is one of the manifestations of old age. There is a gradual intellectual deterioration with impairment of memory, inability to grasp new ideas, slowness in thinking, inattentiveness, and sometimes personality changes, such as egotism, irritability, and suspiciousness. The impairment of memory is usually for recent events, while the events of the distant past are vividly recalled and regaled. Judgment and reasoning are impaired, and imagined slights are greatly resented. Focal evidence of cerebral degeneration occurs. Tremors are common and spasticity and pyramidal tract signs frequently occur. Sometimes the symptoms of paralysis agitans or pseudobulbar paralysis make their appearance.

**Pathological Anatomy**—The brain is small and diffusely atrophied. The convolutions are thin and the sulci are widened, especially in the frontal region. The ventricles are large because of the atrophy of brain substance, and the ependyma becomes granular. Nerve cells are shrunken and atrophied, and many have disappeared. Neurofibrillar degeneration, such as that which occurs in Alzheimer's disease is also seen. There is also increase in neuroglia cells and fibers.

### Pick's Disease

**Synonym**—Lobar sclerosis

**Definition**—Pathologically it is manifested by circumscribed atrophy of one lobe or one hemisphere and usually involves the frontal or temporal region. In advanced cases the entire cortex may show evidence of atrophy. It usually occurs in the later half of adult life and lasts for some years before terminating fatally. There are progressive dementia, an impairment of speech and focal manifestations such as hemiplegia.

### Subacute Combined Degeneration

**Synonym**—Subacute combined sclerosis, posterolateral sclerosis

**Definition**—A progressive disease affecting chiefly the posterior columns and pyramidal tracts in the spinal cord and producing paraesthesia, impairment of position sensibility, ataxia and paraplegia.

**Etiology**—This condition is almost always associated with pernicious anemia. Occasionally it occurs also with hypochromic anemia and with certain toxic and cachectic states.

**Symptoms**—The disease is one of middle age and usually of slow onset. Sensory symptoms appear first and at the beginning are in the nature of paraesthesiae, usually of numbness and tingling in the fingers and toes. Sometimes pains which simulate lightning pains and girdle sensations are also

cases. The intention tremor is absent at rest but when the patient attempts to carry out a movement tremor occurs and becomes progressively more marked as the movement continues. Signs of bilateral pyramidal tract involvement practically always occur in multiple sclerosis. They may not be present in the early exacerbations but some time during the course of the disease they appear



Fig. 46—Section of the spinal cord from a case of disseminated sclerosis. (Pal Weigert stain.) The pyramidal fiber tracts have turned black. The grey matter is unstained except for a few fibers running through it. Multiple patches of degeneration are to be seen in the white matter and a few of these are in the process of degeneration themselves.

**symptoms** If acidosis occurs for any reason this lead will be liberated and then toxic manifestations may arise. The administration of calcium either in food or as a medicine will serve to bind the lead again within the structures noted.

**Symptoms**—Lead neuritis has already been described on page 1094. Cerebral symptoms due to lead may be manifold and show evidence of diffuse involvement of the brain. Acute lead encephalopathy is characterized by convulsions, delirium and coma, and is often associated with signs of increased intracranial pressure and, sometimes, focal symptoms. The differentiation from brain tumor may be difficult. In its more chronic form, lead encephalopathy will manifest mental changes and general systemic symptoms. The general symptomatology of lead poisoning is described in Chapter XXIII. Sometimes lead may produce the symptomatology of localized progressive muscular atrophy involving the small muscles of the hand.

**Pathological Anatomy**—Buzzard and Greenfield regard the symptoms of lead encephalopathy as due to spasms of the arteries in the brain but, in addition to that ganglion cell changes occur and meningeal irritation may be present.

**Prognosis**—The prognosis is always serious, but with proper treatment acute manifestations may improve and complete recovery occur. Chronic symptoms are difficult to improve.

**Treatment**—The treatment of lead poisoning is described in Chapter XXIII.

### Multiple Sclerosis

**Synonyms**—Disseminated sclerosis, insular sclerosis

**Definition**—A chronic disease usually beginning in young people and frequently showing remissions. There are patchy areas of demyelination and gliosis throughout the nervous system and, as a result, the symptomatology is one of disseminated lesions.

**Etiology**—The etiology is unknown, but the condition is believed to be due to an infectious or toxic inflammatory process. The disease is less common in America than in the British Isles and Europe. The age of onset is usually between 20 and 40 years. Males seem to be more frequently affected than females.

**Symptoms**—Since the disease causes an irregular distribution and number of lesions, the symptomatology varies considerably in different cases. Although this is so there are certain groups of symptoms which are rather typical of the disease. The mode of onset varies. Sometimes there is a slow, gradual progression of certain neurological signs but frequently the onset may be manifested by sudden temporary symptoms. It is characteristic that remissions occur. These remissions are usual during the first few years of the disease, but later than this the symptomatology is more likely to be chronic and progressive. On the other hand remissions may last for years. Charcot's triad of symptoms is typical of multiple sclerosis but by no means always occurs. It may become manifest early in the disease or may not appear until considerable progression has taken place. This triad of symptoms consists of nystagmus, scanning, staccato speech and intention tremor. The speech is slow and slurred and scanning and resembles that which occurs in cerebellar



**Symptoms**—The ocular or the myelitic signs may develop first. Some days or weeks may intervene between the two sets of signs or both may occur simultaneously. Usually one eye is affected first and then the disease involves the other eye. There may be a true optic neuritis or a retrobulbar neuritis. Bilateral central scotomata occur and in severe cases blindness may be almost complete. The impairment of vision may be hemianopic in distribution. There is often severe pain in the eyes. The spinal cord lesion is that of a myelitis with level signs of motor and sensory involvement and with loss of sphincter control. There may be an increase of protein and globulin in the spinal fluid and an excess of cells which are usually mononuclear.

**Pathological Anatomy**—There is demyelination of the optic nerves and the spinal cord. The usual location is in the lower cervical and upper dorsal region but the disease may be more diffuse. Perivascular infiltration is present in the demyelinated areas and frequently elsewhere as well.

**Prognosis**—The mortality rate is about 50 per cent which results from respiratory paralysis or infection of the skin or urinary tract. Recovery is often remarkably complete. Relapses do not occur. Treatment is symptomatic.

### Myasthenia Gravis

**Definition**—A chronic disease which is manifested by extreme fatigability of muscles.

**Symptoms**—The diagnosis is not ordinarily difficult. There is an extreme fatigability of muscles which on repeated use may become temporarily paralyzed. The muscles supplied by the cranial nerves are most frequently and most severely affected and for a long time the disability may be confined to them. In the morning after a night's rest there may be no signs of disability but as the day wears on progressive paresis occurs. Ptosis of the eyelids is almost a constant symptom (Fig. 427). Muscles concerned with extraocular movements may fatigue in the same way so that diplopia and strabismus occur after their use and disappear after rest. The muscles of mastication are easily fatigued during the eating of food. The muscles concerned in phonation and articulation tire quickly when the patient talks. Movement of the muscles of the limbs will tire in the same way. The fatigability may become progressively worse until gradually a virtual paralysis exists. Just as voluntary movement tires so does reflex movement fatigue and on repeated tapping of the tendons the reflex responses gradually diminish and finally disappear. The response to faradic stimulation of the muscles shows the same phenomenon and this is called the myasthenic reaction of Joly-Litchard\* has described another abnormality in electrical reaction which is an example of Wedenski inhibition. In the phenomenon of Wedenski inhibition rapid shocks cause a change in nerve endings so that they soon cease to transmit nerve impulses. Pritchard discharges through the patient at varying frequencies a condenser at a potential of 18 volts. Whereas with repetitive stimulation in a normal person a tetanic contraction occurs with a horizontal plateau of maintained maximum tension in myasthenia gravis the maximum tension is not maintained but falls off to a plateau at

Absence of the abdominal reflexes may precede other manifestations by a long period of time. This is followed by the appearance of a plantar extensor reflex on the two sides and the gradual development of signs of a spastic paraplegia. Bladder disturbances occur commonly and may be either retention or incontinence. From involvement of the medulla various cranial nerve paralyses may ensue. Retrobulbar neuritis is one of the most common manifestations of the disease and first shows itself by a pallor of the temporal halves of the optic discs. With this there may be transitory periods of blurring of vision, but complete blindness rarely occurs. Scotomata, enlargement of the blind spot and other visual field defects may be present. Sensory symptoms are not prominent and it has been said that permanent sensory defects do not occur. In most cases parasthesiae are present at some time, most often in the form of numbness. Objective sensory disturbances are usually of position and vibration sensibility and sometimes other forms are impaired as well. Hemiplegia and localized areas of atrophy also occur occasionally. The exacerbations early in the disease may consist of transitory symptoms of sudden onset or the subacute development of symptoms that persist for some time. These may later disappear, during a remission, and when further exacerbations occur, the distribution and type of neurological symptoms may be different. In long standing cases which have progressively become worse, all of the signs mentioned above are usually present. The most characteristic change which occurs in the spinal fluid is the precipitation of colloidal gold in the paretic zone, and this happens in about one half of the cases. The total protein is usually normal.

**Pathological Anatomy**—Scattered throughout the nervous system there are greyish patches of demyelination which are visible macroscopically (Fig 426). In the early stages there is no damage to the axone and this explains why few clinical findings may exist in the presence of many lesions. The areas of degeneration affect principally the white matter, but may occur anywhere and in any size. In older lesions the axones are fragmented and destroyed, and glial proliferation leads to scarring. In some cases there is perivascular infiltration and because of this the condition is often regarded as an infection or inflammation of the central nervous system. The prognosis varies not only may the disease run a long course but remissions may last a long time. The usual course is one of gradual progression. The average duration of life is about eight years.

**Treatment**—There is no adequate nor specific treatment for the disease. Various empirical measures have been used including silver salvarsan, liquor arsenicalis, vitamin B<sub>1</sub>, potassium iodide and pyretic treatment but none of these seems to help.

### Neuromyelitis Optica

**Synonyms**—Diffuse myelitis with optic neuritis, disseminated myelitis with optic neuritis.

**Definition**—A form of subacute encephalomyelitis which runs a self limited course and is characterized by optic neuritis and myelitis.

**Etiology**—The condition seems to be closely related to disseminated sclerosis except that it runs a limited course and has no remissions. It is a rare disease.

lower than maximum tension. This falling off increases with increased frequency of repetition. Remissions and fluctuations in the course of the disease occur and a remission may last for many years. The disease ordinarily begins in the third decade and siblings may be affected. Involvement of the respiratory muscles is very serious and may lead to sudden death.

**Pathological Anatomy**—There is frequently a persistence or hyperplasia of the thymus. In some cases a thymic tumor has been found. There is an infiltration of the muscles and the thymus gland with collections of small cells resembling lymphocytes. These are called lymphorrhages. The glandular elements in the thymus may also proliferate. Lymphorrhages have also been found in other organs.

**Prognosis**—The prognosis is variable. The onset is usually gradual and ocular manifestations such as ptosis and strabismus may be the only signs for years. In some cases where more widespread involvement has existed a remission may occur and leave as residuals only the ocular symptoms.

**Treatment**—The condition is most effectively treated by the use of prostigmine. It is believed that myasthenia gravis is due to excessive action of choline esterase upon acetylcholine at the myoneural junction. Choline esterase is an enzyme normally present in the body which destroys acetylcholine and prostigmine lowers the level of the former in the blood. As a diagnostic test prostigmine solution (1:2000) may be given subcutaneously or intramuscularly in doses of 3 to 5 cc. At the same time atropine sulfate in doses of  $\frac{1}{100}$  or  $\frac{1}{150}$  of a grain should be given to prevent the hyperperistalsis and abdominal discomfort produced by the prostigmine. Within a short time of the injection a startling improvement will occur and this improvement will last for a few hours (Figs 427 and 428). In the treatment of the condition prostigmine is given by mouth in doses of 15 mg. 6 to 9 times in 24 hours. The doses can be spaced so that the greatest effect is produced when it is most needed. When this is given by mouth it is usually not necessary to use atropine although if abdominal discomfort results it can be relieved by tincture of belladonna in small doses. When the respiratory muscles become involved it may be necessary to place the patient in the Drinker respirator and at the same time to use prostigmine subcutaneously.

In many ways myasthenia gravis and myotonia congenita (see page 1047) are physiological opposites. In the former repeated use of the muscle results in rapid fatigue whereas in the latter there is difficulty in muscular relaxation preparatory to movement and repeated movement of the muscle quickly overcomes this difficulty. Furthermore prostigmine which benefits myasthenia aggravates myotonia and quinine which benefits myotonia aggravates myasthenia.

### Progressive Muscular Atrophy and Amyotrophic Lateral Sclerosis

**Definition**—These terms are two of a triad which is used to describe the same disease but to emphasize the structures particularly involved. Progressive muscular atrophy involves primarily the anterior horn cells of the spinal cord, progressive bulbar paralysis involves primarily the motor nuclei in the medulla and amyotrophic lateral sclerosis signifies involvement both of the anterior horn cells and of the Betz cells in the pre-Rolandic motor cortex.



Fig 47—Typical facies of myasthenia gravis with bilateral ptosis and laxity of the muscles about the lip



Fig 48—The same patient as Fig 47 after administration of prothigiline

teriorized. If, however, the flaccid atrophic paralysis in the arms is incomplete then the tendon reflexes may in some cases be increased. The progress of amyotrophic lateral sclerosis is also slow.

**Pathological Anatomy**—Various degrees of degeneration are found in the anterior horn cells many of which have disappeared. Chromatolysis can be seen in the swollen rounded out cells the nuclei of which are pushed to the periphery and are degenerating. Frequently excessive pigment is found in these cells. The nerve fibers in the grey matter of the cord undergo degeneration and the fibers in the anterior roots also. Astrocytic proliferation forms a diffuse scar ring. The involved muscles are also degenerated. Similar changes occur in the motor nuclei in the medulla and in the Betz cells of the motor cortex and there is a secondary degeneration of the pyramidal tract fibers.

**Treatment**—There is no specific treatment for the disease. Rest nursing care and symptomatic treatment are indicated. Recently promising results have been reported following the use of vitamin E (alpha tocopherol) in amounts of 400 m. or more per day. It is the exceptional case however which has shown conspicuous improvement.

### *Dystonia Musculorum Deformans*

**Synonym**—Torsion spasm

**Definition**—A syndrome characterized by involuntary twisting movements which produce torsion of the limbs and trunk.

**Etiology**—The etiology apparently may vary. The disease is not common and has been reported following encephalitis lethargica other degenerative diseases of the basal ganglia and sometimes as a familial disease.

**Symptoms**—In the familial cases the onset is usually early, occurring in childhood or adolescence. The movements consist of rotation or torsion of segments of the body around their long axes. During the movements tonicidity is increased although it may be diminished at other times. The movements resemble those of athetosis. The postencephalitic variety of the disease may be associated also with signs of the Parkinsonian syndrome.

**Pathological Anatomy**—Degeneration in the lenticular nucleus in the corpus luteum and other locations has been described.

**Prognosis**—The familial type is usually fatal within one to six years although cases of survival for as long as thirty years have been described.

**Treatment**—Tincture of stramonium in 10 minim doses three times a day and gradually increasing to 40 or 60 minims three times a day may be of value in some cases. Section of extrapyramidal pathways in the anterior white columns of the spinal cord is a new procedure the value of which has not yet been definitely established.

### *Torticollis*

**Synonym**—Wry neck

**Definition**—Spasmodic or continuous contraction of the cervical muscles producing a rotated attitude of the head. It may occur in organic disease of the nervous system and also as an hysterical condition. In organic disease it may be regarded as a limited form of torsion spasm. It occurs as a symptom

These different types may occur separately, but usually one progresses into the other until all three exist. Thus the disease may begin as progressive muscular atrophy, and in the course of its development show signs of amyotrophic lateral sclerosis and of bulbar paralysis. The usual age of onset is between 30 and 45 years; rarely it is familial. Males are affected more often than females.

**Etiology**—The cause is unknown.

**Symptoms**—The disease develops very slowly with weakness and atrophy in the small muscles of the hands. The process is usually symmetrical and the thenar eminences and interosseous muscles are most severely affected. Deformities of the hand result from contractures of the unaffected muscles, and these vary in type. The atrophy slowly spreads to involve the remainder of the muscles of the hands and gradually extends up the arms to the shoulder girdles. The flexors of the forearm are usually involved before the extensors, and implication of the shoulder muscles causes difficulty in movement at this joint. The deltoid is usually severely affected. Movements of the head become weakened because of involvement of the muscles of the neck. The atrophy may spread down the trunk and the disease tends to have a symmetrical segmental distribution. Fibrillary twitches occur in muscles which are not completely paralyzed. These are due to irritation of the neurones during the slow process of degeneration and consist of fine, rapid, flickering movements in individual muscle fasciculi. Voluntary movement or tapping the muscle may bring these out if they are not otherwise apparent. Since this paralysis is due to a lower motor neurone lesion the reflexes are lost as the disease progresses. Flaccidity is present and the faradic irritability is lost. The disability advances very slowly over a period of years.

When the process passes upward to involve the motor nuclei in the medulla the condition of bulbar paralysis is produced. In this disease there is difficulty in articulation in swallowing and in phonation and these disturbances are known respectively as dysarthria, dysphagia and dysphonia. The tongue becomes atrophied and weak and fibrillary twitches can be seen in it. The vocal cords are parietic and the soft palate is atrophied and paralyzed. Respiratory and cardiac symptoms may occur. The masseter and facial muscles may also become involved. With bulbar paralysis of this type the patient cannot properly chew or swallow food; he cannot move the tongue about in the mouth to keep the latter clean; he cannot clear his mouth of mucus and deposits of food; and he cannot clear his throat by coughing and expectoration. The result is that general nutrition is greatly disturbed and aspiration pneumonia commonly occurs.

In the amyotrophic lateral sclerosis type of the disease the same segmental atrophy, weakness and fibrillations occur. Symptoms previously described are present and in addition there is a spastic paralysis of the legs from involvement of the cells in the motor cortex and degeneration of the pyramidal tracts. This has all the signs of an upper motor neurone lesion. As far as the arms are concerned they have already been involved by a lower motor neurone lesion, which has affected the final common pathway and consequently the superadded symptomatology of amyotrophic lateral sclerosis cannot be ex-

a posterior rhizotomy of the trigeminal nerve by which operation sensory fibers can be divided and motor fibers left intact

*Sphenopalatine Neuralgia*—This is characterized by pain in the eye across the face, behind the ear and radiating into the occiput and down the neck. It is sometimes difficult to differentiate from trigeminal neuralgia and cocainization of the sphenopalatine ganglion may be necessary as a therapeutic test. If this succeeds in abolishing the pain, alcohol injection into the ganglion can be carried out.

*Glossopharyngeal Neuralgia*—The type of pain in this neuralgia is similar to that in trigeminal neuralgia. It usually begins in the side of the throat and radiates down the neck and to the back of the lower jaw. Sometimes it may begin deep in the ear. Swallowing, or protruding the tongue may induce an attack. The treatment is surgical and consists of interrupting the afferent pathway of the painful sensation in the glossopharyngeal nerve.

*Sciatica*—Sciatica is manifested by pain in the distribution of the sciatic nerve. It may be due to neuritis or to neuralgia. It is usually secondary to some other cause such as arthritis, anomalies of the lower lumbar vertebrae, disease of the spine or pelvis, back strain, pelvic conditions and unknown causes. The onset may be severe but is usually gradual. For a time there is only slight pain in the back of the thigh, particularly after exertion or if the leg is held in certain positions. The severity of the pain increases and it radiates down the leg. Pressure on the middle of the thigh, in the gluteal fold and at the sacrosciatic notch causes tenderness. The leg is held flexed at the knee so as to ease the tension on the nerve. The ankle jerk is sometimes diminished or lost. The condition may be intractable and last for months. Recurrences are common. The treatment consists of rest, strapping the back, the use of heat and analgesics, fixation of the legs and diathermy. Any contributing causes should be removed if possible. Injection of normal saline into the nerve sheath or into the epidural space through the sacrococcygeal canal may prove of benefit.

In many cases chronic pain in the back and sciatic neuralgia follow rupture or dislocation of an intervertebral disc (herniation of the nucleus pulposus). This usually occurs in the lumbar region and may be single or multiple. It sometimes follows injury to the back although in some cases such a history cannot be obtained. On x-ray examination in some cases the disc will be found to be narrower than normal and the adjacent vertebral bodies may have a scooped out appearance. By means of the injection of air or lipiodol into the subarachnoid space and then by posturing the patient in a prone position it may be possible to show filling defects due to the protruding disc. Sometimes weakness and atrophy of muscles in the segmental distribution corresponding to the level of dislocation may be found. The treatment of this condition is surgical removal of the dislocated disc.

In the treatment of sciatica the orthopedic surgeon may be called upon to play the chief role. In addition to the eradication of the cause and bed rest, symptomatic treatment such as posturing, warmth and the use of analgesics is of great value. Epidural injection of normal saline and novocaine

in some extrapyramidal syndromes and is not infrequent as a sequela to encephalitis lethargica, in which case it is sometimes associated with the Parkinsonian syndrome

**Symptoms**—The rotation of the head is brought about by contraction of the muscles of the neck and the exact position which the head may assume varies in different cases. The onset of the condition may be gradual or it may begin suddenly. The rotation may occur as a spasmodic symptom or it may be continuous. Frequently the patient will find that placing a finger on the jaw or in the mouth is sufficient to prevent torsion.

**Prognosis**—If the condition is hysterical, proper psychotherapeutic measures should bring about relief. If it is evidence of an organic disease the prognosis is bad. In the organic cases, cutting the anterior and posterior nerve roots and the accessory nerves on the two sides may be carried out but the prognosis is still unfavorable.

### Neuralgia

**Definition**—Intermittent attacks of pain in the distribution of a nerve without evidence of organic disease of the nerve.

**Etiology**—The cause of neuralgia is usually unknown, except in those cases where it is secondary to pressure or local inflammatory changes.

**Symptoms**—The character of the pain varies. The first attack is mild and subsequent attacks increase in intensity. In the same way the attacks increase in duration. Various agents may bring on individual attacks of pain such as local pressure or cold or movement. Muscle spasms occur with the pain, but objective sensory changes are uncommon. Reddening and sweating of the skin may accompany the attack.

**Trigeminal Neuralgia or Tic Douloureux**—This type of neuralgia, which is one of the most common, occurs in the face, in the distribution of the trigeminal nerve. The branch most frequently involved is the second, but the disease may begin in, or spread to, the other branches. The pain occurs in paroxysms and is usually described as stabbing or burning. Usually "trigger zones" occur in the face and touching these or exposing them to a draught will precipitate an attack of pain. The pain is very severe and may be accompanied by a spasm of the face on the affected side and flushing of the skin, lacrimation and salivation. The patient may go for long intervals of time without an attack. The elimination of infections and the administration of bromides and analgesics may cause some improvement. Usually, however, it becomes necessary to carry out some procedure which will interfere with the transmission of pain sensibility from the face to the brain. The simplest procedure is the injection of alcohol into the peripheral branches of the nerve. In the first division this is done in the supraorbital notch; in the second division it is done in the infraorbital foramen; and in the third division it is done in the mental foramen. In some cases also division of the terminal branches of the nerves in the same locations will bring about relief. If these measures are not successful, the maxillary and mandibular nerves may be injected at the foramen rotundum and foramen ovale respectively. Still other cases require



very frequently an increase in the number of attacks either before during or after menstruation. Lennox and Cobb suggest the possibility of an explanation such as the following for the occurrence of convulsions. We know that under sympathetic stimulation contraction of cerebral arteries occurs and we may assume that in epilepsy such contraction may occur. Arterial spasms would lead to decreased blood flow in the capillaries. This might lead to deficient oxygenation and consequently alkalosis of the brain tissue. Under these conditions one might expect an increased passage of fluid outward through the capillary wall with resulting edema. Some or all of these factors (oxygen lack alkalosis edema change in electrolyte equilibrium increased intracranial pressure) might stimulate nerve cells to the point of discharge with resulting muscular spasms. Apnea and muscular contraction would result in a great accumulation of lactic acid and carbon dioxide in the tissues producing a condition of acidosis which would initiate a reversible reaction leading to a better utilization of oxygen a restoration of circulation and relief of muscle spasm.

**Symptoms**—Epileptic attacks may be major or minor the so called 'grand mal' and 'petit mal'. The difference in these two types of attacks is one of severity. Major attacks are usually accompanied by loss of consciousness and by convulsive movements or other symptoms of a disabling type. Minor attacks on the other hand may pass unnoticed and may consist of merely a momentary pause and clouding of consciousness. There are sometimes prodromal manifestations of an approaching epileptic attack so that relatives of the patient may know of its imminence. Such prodromal symptoms may consist of irritability seclusiveness nervousness excessive appetite or some other change the presence of which has become associated with the occurrence of an attack. In addition to this there is usually a warning to the patient or an aura that an attack is about to occur. This warning may last but a moment so little time in fact that the patient cannot prepare for the attack which is to follow. Frequent types of aura are feelings of a rushing sensation a gone feeling or a tremulousness arising in the epigastrium and moving up the body to the head. Sometimes the aura may be felt in the extremities and may be in the nature of paresthesia. Occasionally abdominal pain serves as a warning. In addition to these generalized types of aura there are certain focal auras which have been referred to on page 1009. Following the aura the attack occurs. It is frequently ushered in with a cry and the patient becomes cyanosed or pale and falls unconscious. The limbs stiffen out for a short time and then clonic movements usually begin in the extremities. These movements may be limited or generalized. During the attack the patient frequently bites the tongue between his clenched teeth and incontinence of urine is a common feature. Frothing at the mouth is usually described and this froth may be blood stained if the tongue has been bitten. Following the attack certain sequelae may be present for a variable length of time. Occasionally focal signs such as a Babinski reflex will be present and these are much more likely to follow focal than general attacks. Almost always the patient is drowsy and somewhat confused and usually if it is possible he will sleep for a few hours afterward. The patient himself has no actual knowledge

through the sacral hiatus is used but is usually disappointing. Injection of saline into the sciatic nerve should be done only by one familiar with the procedure.

### Epilepsy

**Definition**—Epilepsy and the convulsive states are symptoms of disease and not disease entities. To define these phenomena is a difficult matter, and Grinker describes them as recurrent paroxysms of convulsive movements, sensory or psychic dysfunction, with or without loss of consciousness.

**Etiology**—Since epileptic phenomena are symptoms, they may be due to many causes. It is probable that there is an inherent convulsive capacity in the constitution of the individual which makes him more liable to manifest certain diseases by this symptom. In the presence of this convulsive capacity the occurrence of other complementary factors may result in the production of epileptic seizures. These additional factors may be many. Gross and microscopic changes in the structure of the brain are often associated with epilepsy. Thus the condition occurs in cases of brain tumor, cicatrices of the brain, general paresis and a multitude of other organic diseases of the nervous system. Physical and chemical factors may also precipitate attacks and these include changes in oxygenation, in acid base equilibrium, in edema of tissues and in the permeability of cell membranes. The circulation is intimately associated with the production of these changes. In addition, disturbances and diseases in other systems of the body are frequently accompanied by epileptic attacks.

**Pathogenesis**—The mechanism of the production of convulsive symptoms is that of a neural discharge at some level of the central nervous system. These discharges need not necessarily arise in the cerebral cortex, as convulsions may occur due to discharges in the spinal cord, as in strychnine poisoning, or in the diencephalon as described by Penfield. The exact physicochemical processes which induce this discharge are not known but there is evidence to indicate that it is concerned with vascular phenomena, acid base equilibrium and the metabolism of water and of electrolytes. That a change in circulation occurs is attested by the fact that vascular phenomena take place in the cortex of the brain coincident with attacks. It has been observed frequently that blanching of the surface of the brain often in a small area occurs immediately before an attack and then as the convulsion begins the blood vessels become congested and suffused. By alteration in acid base equilibrium attacks may be induced or inhibited. Alkalosis is able to produce attacks and this result is hastened if it is combined with overventilation or hyperpnea. Conversely starvation and the maintenance of a mild acidosis may inhibit or even prevent attacks especially in children. Contraction of peripheral vessels has been seen to occur during overventilation and alkalosis. On the other hand the rebreathing of air with a high carbon dioxide content is often sufficient to stop an epileptic attack. The alteration of the metabolism of water and electrolytes by forced hydration is also able to produce attacks. Individual attacks may be precipitated in epileptic patients by undue exertion, mental worry, the use of alcohol, constipation and sometimes by other factors. In women, there is

by the fact that they persist even in curarized animals in which the actual convulsion is prevented. In subclinical or larval grand mal there are random isolated spikes, sharp waves of longer duration and also slow waves. If the attacks are non focal these abnormalities will arise from many points but are not synchronized. If the attacks do arise from a single focus such as in the cases of the gross structural lesions which we have discussed, there will be a phase reversal at this point and therefore the location of the focus can be determined. At the present time there is some dispute as to whether a typical pattern occurs for psychomotor epilepsy and psychic equivalents. Because of these disturbances in cortical rhythm Lennox has proposed the term *cerebral dysrhythmia* as a substitute for the term epilepsy.

Personality changes and psychiatric symptoms frequently occur in epileptics. These do not always bear relation to the duration of the disease to its severity nor to the amount of cortical atrophy that exists. Personality changes are sometimes obviously dependent upon the restricted life that is forced upon the patient and the worries which his illness entails. Apart from this however irritability, seclusiveness, suspiciousness, etc., commonly occur and these in some cases, become so marked as to necessitate institutionalization. Not infrequently, the mental changes may be more severe, and progressive intellectual deterioration will occur and lead to dementia. Epileptic patients with psychoses should be committed to an institution as they are likely to be dangerous if free in the community.

**Treatment**—In those cases of focal epilepsy in which demonstrable focal, structural lesions occur in the brain the treatment consists of surgical removal of these. Such treatment has proved very successful in a large series of cases published by Penfield. Sympathectomy has not proved of value in the treatment of this condition.

The chief medical treatment of the epilepsies is the use of luminal, or phenobarbital. This is given in doses varying from one half grain to 2 grains three times a day. The dose may be modified and given at whatever time and in whatever amount best suits the individual patient. It is sometimes possible by giving a single dose of  $1\frac{1}{2}$  grains at night to control the attacks. Luminal is effective in reducing, and sometimes in stopping major epileptic attacks but its efficacy is much less in regard to minor attacks. The medicine should be taken regularly and no single dose should be missed as this may be followed by an aggravation of the condition and even by status epilepticus. Bromides are sometimes useful adjuvants to luminal but have the disadvantage that when used over a long period of time they lead to a skin rash. In certain cases the use of thyroid extract in addition to the phenobarbital, has produced greater improvement and the dosage and continued use of this should be regulated by frequent determinations of the basal metabolic rate.

A rigidly controlled program of dehydration has been adopted and recommended in the treatment of chronic epilepsy by Fay. He recommends a total fluid intake of from 300 to 500 cc per 24 hours depending upon the severity and number of attacks. This fluid intake is given in small amounts equally divided during the day so as to minimize the severe thirst of which these patients complain. No sodium chloride is added to the dry diet. The dehydra-

to 3,000 6,000 c.c. in 24 hours or until a satisfactory attack occurs (5) Diet to contain considerable amounts of carbohydrates such as vegetables ice cream, custard, fruits, potatoes rice, candy, cereals, etc. This may be divided into three roughly equal meals (6) Fluid intake and output to be carefully measured for each six hour period and charted against weight (7) Nausea dizziness, vomiting, weakness, dropping blood pressure, fainting, syncope to be particularly noted. If these occur, the procedure should be stopped.

X ray examination of the skull after the injection of air into the lumbar subarachnoid space or directly into the ventricles has already been referred to on page 1031. By this means it is usually possible in focal structural lesions to determine the location of the lesion. Such a result, in cases with attacks suggesting the same focus, is an indication for surgical intervention. It is frequently found both in the presence and absence of focal structural changes that the ventricular system is enlarged and that the brain shows evidence of diffuse atrophy either on one side or throughout (Fig. 429).

More recently electroencephalography has been added to our methods of examination. This method of investigation consists in recording electrically the waves of action potentials from the cellular areas of the brain and especially from the cerebral cortex. In 1924 Berger described the so called alpha rhythm from the occipital cortex. These rhythmic discharges occurred from 8 to 12 times per second and they were present when the eyes were closed. They varied in amplitude in different individuals but they were constant in each individual. If the individual opened his eyes or engaged in some mental activity such as anxiety or a mental problem, the alpha rhythm was blocked out. Since that time investigations have gone on, and it has been found that in addition to the normal alpha rhythm which occurs in the posterior parts of the hemispheres there is a different sort of rhythm called beta rhythm which can be recorded from the anterior half of the brain. This latter is of lower amplitude than alpha rhythm and it occurs more rapidly—about 20 to 30 times per second. It is not blocked out by mental activity as the alpha rhythm is. Disease processes cause changes in the amplitude rate and shape of these waves. In subdural effusion and meningeal tumors for example where the brain surface is pushed away from the skull there is a depression of activity. On the other hand in traumatic or degenerative cerebral lesions so called delta waves appear which are of greater amplitude than the normal and which occur from one to seven times per second.

There are several types of abnormal wave produced in the epileptic state. In petit mal for example there is the appearance of a sharp spike wave and of the delta wave just described and these abnormalities occur in rhythmic pattern. They can be recorded especially from a basal lead attached to the posterior wall of the nasopharynx and it is likely that they originate at the base of the brain or in the hypothalamic region. These sequences of spikes and slow waves appear at the rate of 3 per second. In grand mal attacks rapid sharp waves of high amplitude occur in rhythm and they vary in frequency. They seem to consist of a hypersynchrony produced by an excessive number of cells acting together. That the tremors are not due to the muscular movements nor to afferent impulses arising from them is shown

by the fact that they persist even in curarized animals in which the actual convulsion is prevented. In subclimic or larval grand mal there are random isolated spikes, sharp waves of longer duration and also slow waves. If the attacks are non focal these abnormalities will arise from many points but are not synchronized. If the attacks do arise from a single focus such as in the cases of the gross structural lesions which we have discussed there will be a phase reversal at this point and therefore the location of the focus can be determined. At the present time there is some dispute as to whether a typical pattern occurs for psychomotor epilepsy and psychic equivalents. Because of these disturbances in cortical rhythm Lennox has proposed the term cerebral dysrhythmia as a substitute for the term epilepsy.

Personality changes and psychiatric symptoms frequently occur in epileptics. These do not always bear relation to the duration of the disease, to its severity nor to the amount of cortical atrophy that exists. Personality changes are sometimes obviously dependent upon the restricted life that is forced upon the patient and the worries which his illness entails. Apart from this however irritability, seclusiveness, suspiciousness, etc. commonly occur and these in some cases become so marked as to necessitate institutionalization. Not infrequently the mental changes may be more severe, and progressive intellectual deterioration will occur and lead to dementia. Epileptic patients with psychoses should be committed to an institution as they are likely to be dangerous if free in the community.

**Treatment**—In those cases of focal epilepsy in which demonstrable focal structural lesions occur in the brain the treatment consists of surgical removal of these. Such treatment has proved very successful in a large series of cases published by Penfield. Sympathectomy has not proved of value in the treatment of this condition.

The chief medical treatment of the epilepsies is the use of luminal or phenobarbital. This is given in doses varying from one half grain to 2 grains three times a day. The dose may be modified and given at whatever time and in whatever amount best suits the individual patient. It is sometimes possible by giving a single dose of  $1\frac{1}{2}$  grains at night to control the attacks. Luminal is effective in reducing and sometimes in stopping major epileptic attacks but its efficacy is much less in regard to minor attacks. The medicine should be taken regularly and no single dose should be missed as this may be followed by an aggravation of the condition and even by status epilepticus. Bromides are sometimes useful adjuvants to luminal but have the disadvantage that when used over a long period of time they lead to a skin rash. In certain cases the use of thyroid extract in addition to the phenobarbital has produced greater improvement and the dosage and continued use of this should be regulated by frequent determinations of the basal metabolic rate.

A rigidly controlled program of dehydration has been adopted and recommended in the treatment of chronic epilepsy by Fay. He recommends a total fluid intake of from 300 to 500 cc per 24 hours depending upon the severity and number of attacks. This fluid intake is given in small amounts equally divided during the day so as to minimize the severe thirst of which these patients complain. No sodium chloride is added to the dry diet. The dehydra-

tion method in practical use has given less favorable results in the experience of others than those reported by Fay

In 1937 Putnam and Merritt began a series of experiments to determine the anticonvulsant powers of a group of old and new drugs. They carried out their experiments by determining the electrical threshold in the cat, and then studying changes which might be brought about in this threshold by the administration of various drugs. The well known anticonvulsants of course raised the threshold, and these included the bromides and phenobarbital

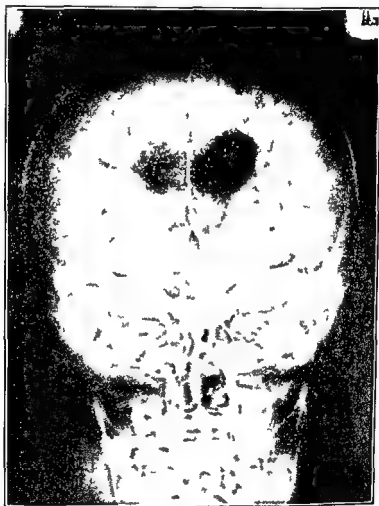


Fig. 49.—Generalized cerebral atrophy in a case of epilepsy without a focal lesion obstructing the escape of cerebrospinal fluid from the ventricle. The lateral ventricles and third ventricle are greatly enlarged, symmetrical and in the midline.

They found in addition, however, a small series of drugs which seemed to be of greater anticonvulsant effect than phenobarbital and which had relatively low toxic effect. From this work the development of a new drug, sodium diphenylhydantoinate (dilatant) arose and it has attained widespread use. It is reasonably well tolerated by most patients who find it of considerable subjective as well as objective benefit. It is a more effective anticonvulsant than phenobarbital and is accompanied by fewer depressing effects; its toxic manifestations are relatively slight and many of them pass off spontaneously within a period of three or four weeks and it—like all other

anticonvulsants in common use—is much less effective in the treatment of petit mal than of grand mal. It may be found that the effective dose closely approximates the toxic which is indicated by tremors, nystagmus, gastric discomfort and skin rashes. A hyperplasia of the gums is apt to occur especially in children. Other less common signs of toxicity are fatigue, loss of weight, emotional and physical excitability and hirsutism.

Dilantin is usually given in doses of  $1\frac{1}{2}$  grains three to five times a day. If given with meals its moderately unpleasant effects are diminished. Usually a small dose of phenobarbital is continued. Any changes in the medical treatment of epilepsy should be made slowly and gradually.

In children the most efficacious treatment is by means of ketosis or acidosis, and this, in its own field, is probably the most satisfactory single means of treating epilepsy. The diet is based upon the keto<sub>2</sub>genic antiketogenic ratio of the foods given. The caloric requirements of the child are determined by the standard methods based upon body surface. Sufficient protein is given to preserve nitrogen equilibrium and the balance of the caloric requirements is made up by the administration of carbohydrate and fat. The keto<sub>2</sub>genic antiketogenic ratio should be three or more to one. Carbohydrate is made up of 100 per cent antiketogenic element. Fat consists of 90 per cent keto<sub>2</sub>genic and 10 per cent antiketogenic elements. Protein consists of 58 per cent antiketogenic and 44 per cent keto<sub>2</sub>genic elements (according to Woodyatt's formula).

At the beginning the keto<sub>2</sub>genic antiketogenic ratio may be gradually established. Examination of the urine for ketone bodies, at regular intervals will indicate whether ketosis is being satisfactorily maintained.

### Synonym.—Hemicrania Migraine

**Definition**—Paroxysmal attacks of headache which is usually situated in one side of the head and frequently associated with visual disturbances, nausea and vomiting. It may occur as an hereditary disorder.

**Etiology**—The etiology of this condition is unknown. It has been ascribed to arterial spasms and to localized cerebral edema. Occasionally association of migraine and epilepsy has been described and these conditions are regarded as bearing some relationship to one another. Women are more subject to the disease than men and it usually begins shortly after puberty.

**Symptoms**—The attack may be preceded by prodromal symptoms. Headache may be the only manifestation and usually involves the entire half of the head. It is of a boring throbbing character. Nausea is usually present and vomiting may occur. In some cases the vomiting relieves the attack. Visual phenomena frequently occur and are usually manifested in the opposite hemianopic field. At the beginning they may consist of flashes of light or of an expanding bright spot and this is followed by blurring of vision or blindness in the involved field. Paresthesia and weakness of the opposite side of the body may also occur. The attacks are frequently associated with the menstrual period.

Ophthalmoplegic migraine is a special form associated with ocular paralysis which may persist for days or weeks after the attack has subsided. This occurs uncommonly and the diagnosis should be made with caution.

**Treatment**—The subcutaneous injection of ergotamine tartrate 0.5 mg will often stop the attack. Sometimes a second dose is necessary. The drug is not as efficacious by mouth, but may be tried. Emmenin, in doses of  $\frac{1}{2}$  to 1 drachm twice daily in the intermenstrual period, will also prevent attacks in some patients.

### Narcolepsy

**Synonym**—Gelineau's disease

**Definition**—A condition manifested by sudden irresistible attacks of sleep and sometimes by attacks of hypotonia associated with emotional outbursts and sufficient to make the patient fall to the ground (cataplexy).

**Symptoms**—Little can be added to the definition above. The patient with this condition may manifest only narcoleptic attacks, or only cataplectic attacks, or a combination of both. The last is the usual condition. The narcoleptic attacks consist of an irresistible attack of somnolence. The patient will go to sleep while in the midst of an occupation or conversation. The cataplectic attack usually occurs when the patient's emotions are aroused and especially in the presence of pleasurable emotions. Consequently, the phenomena often occur when the patient is induced to laughter. The body musculature grows flaccid, the mouth droops open and the legs bend under the patient so that he slowly and limply sinks to the ground. Consciousness is retained.

**Treatment**—The best therapeutic results seem to follow the use of ephedrine. The initial dose should be gr  $\frac{1}{4}$  of ephedrine sulfate three times a day, and this may be increased if necessary. Recently it has been found that benzedrene sulfate in doses of 10 mg, once twice or three times a day may also be of great value in the treatment of this condition. If it is given late in the day this drug will produce insomnia. It also tends to raise the blood pressure so that the condition of the cardiovascular system of the patient should be watched.

### References

- Abramson, I. L. Acute Lymphocytic Meningitis. *Arch Neurol & Psychiat* 31: 5, 1914.  
 Adson, A. W. The Diagnosis and Treatment of Protruded or Ruptured Intervertebral Disks as a Cause for Low Back Pain and Sciatica. *Proc Interst Podiatr M. A. North America* pp 196-201, 1942.  
 Arey, L. B. Developmental Anatomy. Philadelphia, 1930. W. B. Saunders Co.  
 Armstrong, C., and Diekens, F. Benign Lymphocytic Choriomeningitis (Acute Aseptic Meningitis). *Pub Health Rep U. S. Treasury Dept* 50: 831, 1935.  
 Atkinson, Miles. Diagnosis and Treatment of Meniere's Syndrome. *Arch Otolaryng* 37: 40-53, 1943.  
 Bailey, P. Intracranial Tumor. Springfield, Ill., 1933. Charles C. Thomas.  
 Bailey, P. and Cushing, H. Tumors of the Gloma Group. Philadelphia, 1926. J. B. Lippincott Co.  
 Benda, C. E. and Cobb, S. On the Pathogenesis of Paralysis Agitans (Parkinson's Disease). *Medicine* 21: 75, 1942.  
 Boyd, Wm. Pathology of Internal Diseases. Philadelphia, 1931. Lea & Febiger.  
 Brain, W. R. Diseases of the Nervous System. London, 1933. Oxford University Press.  
 Burdick, W. F., Whipple, D. V. and Freeman, W. Amyotonia Congenita (Oppenheim). Report of Five Cases With Necropsy. Discussion of the Relationship Between Amyotonia Congenita, Werdnig-Hoffman Disease, Neonatal Polomyelitis and Muscular Dystrophy. *Am J Dis Child* 69: 295-307, 1945.



- Buzzard E F and Greenfield J G Pathology of the Nervous System London, 1921 Constable & Co Ltd
- Calvinander W B Diseases of the Spinal Cord Baltimore 1932 Williams & Wilkins Co
- Cannon W B The Wisdom of the Body New York 1932 W W Norton & Co Inc
- Cone W V Acute Pathological Changes in Neuroglia and in Microglia Arch Neurol & Psychiat 20 341 1938
- Cowdry P V Special Cytology Vol 2 New York 1929 Paul B Hoeber Inc
- Cushing H Situatory Body Hypothalamus and Parasympathetic Nervous System Springfield Ill 193 Charles C Thomas
- Danly W I Intracranial Arterial Incurvum Ithaca N Y 1944 Comstock Publishing Co Inc
- Eisberg C A Some Features of the Gross Anatomy of the Spinal Cord and Nerve Roots and Their Bearing on the Symptomatology and Surgical Treatment of Spinal Disease Am J M Sc 144 99 1912
- Eisberg C A Tumors of the Spinal Cord New York 1929 Paul B Hoeber Inc
- Evan J I Experimental Epilepsy (Thesis) Dept of Neurology and Neurosurgery Montreal 1930 McGill University
- Evan J P A Study of the Sensory Defects Resulting from Lesion of Cerebral Substance in Humans Association for Research in Nervous and Mental Diseases Vol 10 Baltimore 1933 William & Wilkins Co
- Gibbs F A and Gibbs E L Atlas of Electroencephalography Cambridge Mass 1941 C V Cumming p 1
- Gordon M H Nat Health Ins Med Research Comm Spec Report Series London 3 10 1917
- Greenfield J G and Carmichael E A The Cerebrospinal Fluid in Clinical Diagnosis London 1929 The Macmillan Co
- Gruinker R R Neurology Springfield Ill 1934 Charles C Thomas
- Hart M The Psychology of Insanity Cambridge 1933 Cambridge University Press
- Healy W Browner A F and Bowers A M The Structure and Meaning of Psychoanalysis New York 1930 Alfred A Knopf Inc
- Hirsch A Handbuch der histologische pathologie ed 2 Stuttgart F Enke 1896 3
- Jasper H H Electrical Signs of Cortical Activity Arch Bull 34 411 481 1937
- Jasper H H Electroencephalography Chap XIV in Penfield and Erickson Epilepsy and Cerebral Localization Springfield 1941 Charles C Thomas
- Jasper H H and Herman J Electroencephalography Progress in Neurology and Psychiatry New York 1944 Grune & Stratton p 3-4
- Johnson J W Jr Infectious Polioencephalitis Arch Conf Army Physicians MTO 109 110 1906 14
- Kabat E A Vo re D H and Laxlow H Electrophoretic Study of Protein Components in Cerebrospinal Fluid and Their Relation to Serum Proteins J Clin Investigation 21 1 1942
- Kapper C U Ariens Huber G C and Crosby E C The Comparative Anatomy of the Nervous System of Vertebrates Including Man 2 Vols New York 1930 The Macmillan Co
- Holmer J A Rule A M and Madden B Chemotherapy and Serum Therapy of Pneumococcus and Streptococcus Meningitis Cerebral Cisternal Spinal Lavage Method of Treatment of Septic Meningitis Arch Otolaryng 9 478 1929
- Fennox W G and Cobb S Epilepsy Baltimore 1938 Williams & Wilkins Co
- Filhe R D Histopathologic Reaction to the Virus of Lymphocytic Choriomeningitis in the Chick Embryo Pub Health Rep U S Treasury Dept 51 41 1936
- Indley Donald Electroencephalography Chap 13 in Hunt J McT Personality and Behavior Disorders New York 1944 The Ronald Press
- Macleod J J R Physiology in Modern Medicine ed 7 St Louis 1933 The C V Mosby Co

**Treatment**—The subcutaneous injection of ergotamine tartrate 0.5 mg will often stop the attack. Sometimes a second dose is necessary. The drug is not as efficacious by mouth, but may be tried. Emmenm, in doses of  $\frac{1}{2}$  to 1 drachm twice daily in the intermenstrual period, will also prevent attacks in some patients.

### Narcolepsy

**Synonym**—Gelineau's disease

**Definition**—A condition manifested by sudden irresistible attacks of sleep and sometimes by attacks of hypotonia, associated with emotional outbursts and sufficient to make the patient fall to the ground (cataplexy).

**Symptoms**—Little can be added to the definition above. The patient with this condition may manifest only narcoleptic attacks or only cataplectic attacks or a combination of both. The last is the usual condition. The narcoleptic attacks consist of an irresistible attack of somnolence. The patient will go to sleep while in the midst of an occupation or conversation. The cataplectic attack usually occurs when the patient's emotions are aroused and especially in the presence of pleasurable emotions. Consequently the phenomena often occur when the patient is induced to laughter. The body musculature grows flaccid, the mouth droops open and the legs bend under the patient so that he slowly and limply sinks to the ground. Consciousness is retained.

**Treatment**—The best therapeutic results seem to follow the use of ephedrine. The initial dose should be gr  $\frac{1}{4}$  of ephedrine sulfate three times a day and this may be increased if necessary. Recently it has been found that benzedrene sulfate, in doses of 10 mg once twice or three times a day may also be of great value in the treatment of this condition. If it is given late in the day this drug will produce insomnia. It also tends to raise the blood pressure so that the condition of the cardiovascular system of the patient should be watched.

### References

- Abramsen T I. Acute Lymphocytic Meningitis. *Arch Neurol & Psychiat* 31: 1-5, 1944.  
 Adson A W. The Diagnosis and Treatment of Protruded or Ruptured Intervertebral Disks as a Cause for Low Back Pain and Sciatica. *Proc Internat Congrat N A North America* pp 196-201, 1942.  
 Arey, L B. Developmental Anatomy. Philadelphia, 1930. W B Saunders Co.  
 Armstrong C and Diekens F. Benign Lymphocytic Choriomeningitis (Acute Aseptic Meningitis). *Pub Health Rep U S Treasury Dept* 50: 831, 1935.  
 Atkinson Miles. Diagnosis and Treatment of Meniere's Syndrome. *Arch Otolaryng* 37: 40-53, 1943.  
 Bailey P. Intracranial Tumor. Springfield, Ill 1943. Charles C Thomas.  
 Bailey P and Cushing H. Tumors of the Gloma Group. Philadelphia, 1926. J B Lippincott Co.  
 Bender C E and Cobb S. On the Pathogenesis of Paralysis Agitans (Parkinson's Disease). *Medicine* 21: 1, 1942.  
 Boyd Wm. Pathology of Internal Diseases. Philadelphia, 1931. Lea & Febiger.  
 Brain W R. Diseases of the Nervous System. London, 1933. Oxford University Press.  
 Burdick W F, Whipple D V and Freeman W. Amyotonia Congenita (Oppenheim). Report of Five Cases With Neurological Discussion of the Relationship Between Amyotonia Congenita, Werdnig-Hoffman Disease, Neonatal Ichthyosis and Muscular Dystrophy. *Am J Dis Child* 69: 225-267, 1942.

## CHAPTER XVI

### PSYCHOSOMATIC MEDICINE

FREDERICK R. HANSON B.Sc. M.D.

#### INTRODUCTION

During recent years the term psychosomatic has appeared in medical literature with an increasing frequency and there is every reason to believe that the attention given to this phase of medical evolution will continue to increase. In spite of this increasing interest or perhaps because of it a considerable confusion has arisen not only about the meaning of the term psychosomatic but also about the basic changes in medical concepts involved in the acceptance of the role played by emotional stresses in the processes of disease. It is very difficult to give a clear comprehensive definition of the meaning of psychosomatic in a few words. For purpose of convenience in this book the term psychosomatic medicine will have the meaning of

An integrated approach to the study of disease which properly evaluates the psychological, somatic and environmental factors involved in the process of disease in the living person.

Although the term is relatively new having been first brought into common usage by Draper as *psysomatic* in 1928 the necessity of studying and treating the person as well as the so-called disease has been recognized for over two thousand years. While the necessity of a holistic approach to the study of disease has been expressed frequently by many physicians during that time such an approach has lain within the realm of the Art of Medicine until the beautiful studies of Cannon in 1908 first presented objectively the fact that there was a close relationship between the emotional state of the animal and its physiological processes. Subsequent to Cannon's initial work an increasing number of animal and human experiments demonstrated clearly that emotional factors play a definite role not only in laboratory studies but in the disease process of the living human being as well. The scope of this book does not permit the detailing of these experimental and clinical studies but they can be found in the standard texts and scientific periodicals on psychosomatic medicine.

During the latter part of the nineteenth century an equally important series of developments began to occur in the field of psychiatry. Prior to that time the studies of the human mind and emotions had been based upon concepts which were variously mystical, demonstric or religious in origin. Starting from his interests in the biological medicine of that time Freud became increasingly aware of the fact that emotional factors played a powerful role in the life and well being of the individual. It was forced upon him that these emotional disturbances were poorly understood but that more importantly it was possible to understand these disturbances in terms which were at once both logical and useful in therapy. The monumental investigations of Freud

- Montreal Neurological Institute Neurological Biographies and Addresses London 1936 Oxford University Press
- Moore J F The Modern Treatment of Syphilis, Springfield, Ill 1923 Charles C Thomas
- Neal J H Experience of Meningitis Division of New York Department of Health, Am J Pub Health 21 147 1931
- Netter, A, and Debré R Ménigite Cerebrospinale, Paris, 1911, Masson et Cie
- Nonne, M Über einen klinisch und Anatomisch untersuchten Fall von Meningitis Cerebrospinalis acuta Syphilitica (mit positivem Spirochätenbefund) im Frühstadium der Lues, Med Klin 17 1501, 1921
- Peet, M M Advanced Meningococcus Meningitis Treatment by Combined Ventricular, Cisternal and Lumbar Punctures, J A M A 86 1818, 1926
- Penfield W G Cytology and Cellular Pathology of the Nervous System, 3 vols, New York 1932 Paul B Hoeber Inc
- Penfield W C Principles of the Pathology of Neurosurgery Nelson Loe's Lect Surgery 1927, p 303
- Penfield, W G Evans J P and MacMillan, J A Visual Pathways in Man With Particular Reference to Macular Representation Arch Neurol & Psychiat 33 816 1935
- Pullen R I, and Bodeman W A Infectious Polyncuritis (Guillain Barre Syndrome) Am J M Sc 211 110 1946
- Ranson S W Anatomy of the Nervous System, Philadelphia 1931 W B Saunders Co
- Ray Bronson S Differential Diagnosis Between Ruptured Lumbar Intervertebral Disk and certain Diseases of the Spinal and Peripheral Nervous Systems, S Clin North America 28 27-31 1946
- Sophian, A Epidemic Cerebrospinal Meningitis, St. Louis 1913 The C V Mosby Co
- Stookey P F Elliott B F and Teachenor F R Mechanism of Spinal Block in Epidemic Meningitis, J A M A 95 106 1930
- Strecker D A and Lbaugh, I G Practical Clinical Psychiatry, ed 4, Philadelphia 1930 P D Davidson's Son & Co
- Talbot J H Periodic Paralysis A Clinical Syndrome, Medicine 20 80 143 1941
- Tilney F and Riley H A The Form and Functions of the Central Nervous System New York 1923 Paul B Hoeber Inc
- Tomney J A Acute Lymphocytic Meningitis J Pediat 3 148, 1936
- Turner A I and Reynolds F D Intracranial Pyogenic Diseases Edinburgh 1931 Oliver & Boyd
- Viets Henry R Myasthenia Gravis Treated With Large Doses of Neostigmine Methyl sulfate Intramuscularly and Intravenously and With Neostigmine Bromide Orally Am J M Sc 208 701-08 1944
- Villiger L Brain and Spinal Cord translated by G A Liervol Philadelphia 1918, J B Lippincott Co
- Wadsworth, A Meningococcus Meningitis Results of Recent Investigation in Relation to Serum Therapy Am J Hyg 14 630 1931
- Webber E G Cerebrospinal Meningitis Boston M & S J 18 667 75 29 59 80 etc
- Wechsler I S A Textbook of Clinical Neurology, ed II Philadelphia, 1935 W B Saunders Co
- Wechsler, I S Recovery in Amyotrophic Lateral Sclerosis Treated With Tocopherols (Vitamin E) Preliminary Report J A M A 114 948 1940
- Weil A A Textbook of Neuropathology Philadelphia 1933 Lea & Febiger
- Weisenburg I and McBride K Aphasia London 1930 Humphrey Milford Co
- White J C The Autonomic Nervous System New York 1930 The Macmillan Co
- Wilson, S A Modern Problems in Neurology Baltimore 1929 William Wood & Co
- Wright, S Applied Physiology London 1932 Oxford University Press
- Wyllie W G Clinical Review of Encephalitis Practitioner 148 111 116 1941
- Young A W Involuntary Movements Canad M A J 30 430 1934

ways be considered normal for each individual or each environmental circumstance. For example it may be entirely normal for a student to exhibit a mild diarrhea under the stress of an all important final examination whereas it would be entirely abnormal if he were to develop diarrhea each time he was subjected to the minor stress of being called upon to recite in the classroom, or if his diarrhea were to persist for months after the examination. To state the matter another way if a small harmless snake were to crawl into a room one person might react with utter panic another with slightly fearful avoidance and a third person walk over and pick up the snake. It is obvious that this snake had an entirely different meaning for each of these individuals and that his reaction was based not just on the presence of a snake but much more importantly upon the psychological meaning of the snake to him. By extending this concept it becomes apparent that the reaction of an individual to a given stimulus is dependent upon the psychological meaning of that stimulus to the individual. This concept is one of the utmost importance in the proper understanding of the psychological factors involved in psychosomatic medicine. It immediately brings up the question "How then are these meanings developed in the individual?"

To answer this question completely would take us deep into the fields of psychology and psychiatry and even now some of the factors involved are not fully understood. It will be possible however to discuss some of the more salient features of this process particularly as they pertain to psychosomatic considerations. To begin with it must be recalled that when the infant is born into the world he is still entirely unequipped for independent existence. He must depend upon others not only for food and protection and affection but even for life itself. He is capable only of the most primitive metabolic and gross regulative processes of ingestion and excretion of food and fluids of incoordinated movement of primitive sensory discrimination and of crying. His nervous system is only partially myelinated and he is incapable of coordinated movement speech or verbal understanding. He appears to be aware only of internal stimuli such as hunger and thirst and of external stimuli of a crude nature such as those productive of pain or gross discomfort. Furthermore it is highly improbable that the infant in his early stages of existence can distinguish between what is external and what is internal in origin. The only means of expression available to him are those of crying, wriggling, sleeping and those are primarily of a reflex nature. He must be cared for by a parent or some parent substitute if he is to survive.

It must not be forgotten however that he brings with him certain biochemical and structural mechanisms and propensities of an inherited and congenital origin. These mechanisms plus the unlearned reflexes constitute the basic reactive unit the infant. Whether or not there are also present certain psychological propensities of a basic and individually unlearned nature is a matter of debate at the present time. In any event more recent thinking has indicated that the biochemical psychological and reflex mechanisms present at birth and now considered instinctual may be subject to alteration by environmental influences both physical and psychological during the life of the individual.

and his school, Janet, Bleuler, Jung, Meyer, and others made it clear that the human mind and emotions were provinces open to the tools of scientific investigation. It was this development in the knowledge of individual psychodynamics and the contemporary demonstration of the fact that the emotional and physiological status of the individual were interdependent which gave rise to the objective concepts of psychosomatic medicine.

Many misconceptions have arisen about psychosomatic medicine. To some it is a specialty; others believe that its concepts apply only to certain disorders and still others express the rather naive fear that its proponents believe that all disease is purely psychological in origin. None of these beliefs is correct. Psychosomatic medicine is, in simple terms, the correct practice of medicine, whether it be practiced by the general practitioner, the surgeon, the internist or the psychiatrist. It is essential in the correct practice of medicine that a proper evaluation be given to the role played by somatic, environmental, and psychological factors in every disorder and in every patient. No other approach can lead to clear understanding, accurate diagnosis, and successful therapy.

In order to exemplify this let us consider the disorder asthma. In most cases there is a protein sensitivity in abnormal biochemical mechanism which is present in a variable intensity and which is often inherited. But this sensitivity is not in itself enough for the individual must come into contact with the antigen to which he is sensitive before an attack will occur; thus we see environmental factors coming into consideration. Further, we find from observation that many of these individuals will have their attacks markedly intensified or even precipitated by powerful emotional stress. The importance of any one of these factors may vary considerably from individual to individual and may even vary markedly from time to time in the same individual. It is thus apparent that any clear understanding of the disease and proper diagnosis of the patient will involve consideration of the somatic (sensitivity), environmental (presence of exciting antigen) and psychological (intensifying or precipitating emotional conflicts) factors. Furthermore therapy cannot be effective without desensitization or removal of the antigen and alleviation of the related emotional stresses.

In consideration of the fact that the epidemiological and somatic factors of disease will be discussed in detail elsewhere in this textbook the remainder of this section will be devoted primarily to the discussion of psychological considerations.

### PSYCHOLOGICAL CONSIDERATIONS

It is implicitly recognized by most physicians that emotional disturbances may influence the many organ functions of the body. We are all familiar with the blushing of the embarrassed young girl, the pallor and cold sweat of fear, the urinary or bowel frequency of the student at examination time, the indigestion of disgust and the apoplectic countenance of rage. These are all concomitants of everyday living and all may be perfectly normal phenomena. Although these psychophysiological phenomena are universally present in mankind in one form or another it does not follow that their appearance must be

ways be considered normal for each individual or each environmental circumstance. For example, it may be entirely normal for a student to exhibit a mild diarrhea under the stress of an all important final examination, whereas it would be entirely abnormal if he were to develop diarrhea each time he was subjected to the minor stress of being called upon to recite in the classroom or if his diarrhea were to persist for months after the examination. To state the matter another way, if a small harmless snake were to crawl into a room one person might react with utter panic, another with slightly fearful vocalization, and a third person walk over and pick up the snake. It is obvious that this snake had an entirely different meaning for each of these individuals and that his reaction was based not just on the presence of a snake but much more importantly upon the psychological meaning of the snake to him. By extending this concept it becomes apparent that the reaction of an individual to a given stimulus is dependent upon the psychological meaning of that stimulus to the individual. This concept is one of the utmost importance in the proper understanding of the psychological factors involved in psychosomatic medicine. It immediately brings up the question: How then are these meanings developed in the individual?

To answer this question completely would take us deep into the fields of psychology and psychiatry and even now some of the factors involved are not fully understood. It will be possible, however, to discuss some of the more salient features of this process particularly as they pertain to psychosomatic considerations. To begin with it must be recalled that when the infant is born into the world he is still entirely unequipped for independent existence. He must depend upon others not only for food and protection and affection but even for life itself. He is capable only of the most primitive metabolic and gross regulative processes of ingestion and excretion of food and fluids of incoördinate movement of primitive sensory discrimination and of crying. His nervous system is only partially myelinated and he is incapable of coördinated movement, speech or verbal understanding. He appears to be aware only of internal stimuli such as hunger and thirst and of external stimuli of a crude nature such as those productive of pain or gross discomfort. Furthermore it is highly improbable that the infant in his early stages of existence can distinguish between what is external and what is internal in origin. The only means of expression available to him are those of crying, writhing, sleeping and those are primarily of a reflex nature. He must be cared for by a parent or some parent substitute if he is to survive.

It must not be forgotten, however, that he brings with him certain biochemical and structural mechanisms and propensities of an inherited and congenital origin. These mechanisms plus the unlearned reflexes constitute the basic reactive unit, the infant. Whether or not there are also present certain psychological propensities of a basic and individually unlearned nature is a matter of debate at the present time. In any event more recent thinking has indicated that the biochemical, psychological and reflex mechanisms present at birth and now considered instinctual may be subject to alteration by environmental influences both physical and psychological during the life of the individual.

Whatever disagreements there may be over the hypothetical backgrounds of such complex matters as instincts and heredity, there is little disagreement about the observed activity and rapid progress of the infant, both physically and psychologically. In a short time he begins to respond selectively to move in a coordinated and purposeful fashion to be aware of his surroundings, and to identify individuals. Since he is fed, cared for, and soothed by his mother or some mother figure, what is more natural than that his first awareness of a world outside himself and his first experiences of affection should be personified in his mother. Indeed there is strong evidence to indicate that the infant makes little differentiation in such apparently disparate manifestations as the satisfaction of being fed, warmth, affection, and mother. It must also be added that there is now evidence that the assumption of hunger without the accompaniment of physical manifestations of affection can lead to serious psychological and physical disability for the infant. These points are of real importance in psychosomatic medicine and psychiatry because this equation of physical and psychological satisfactions contains not only the seeds of future emotional conflicts but also may be of considerable importance in establishing a permanent relationship between an emotional conflict and the physiological disturbance of a specific organ system, a point which will be discussed later in more detail.

In the earliest postpartum stage of the infant's development, a period of a year or more, the most important source of comfort and discomfort, satisfaction and dissatisfaction is centered around the problem of feeding. Not only does his life and well-being depend upon food but when he is hungry he is uncomfortable and when he is fed he becomes comfortable and satisfied. In all probability the infant is aware of existence only in terms of his own feeling of comfort or discomfort at this stage of his development. As he develops he begins to equate being fed with the feeling of satisfaction and being hungry with dissatisfaction. With the increasing development of his perceptual senses and probably because there is some delay in the satisfaction of his hunger, he begins to become aware of the fact that being fed and being satisfied are dependent upon some agency outside of himself. This agency is the mother or some similar person. During this same early phase in development, observation of the infant indicates that he derives a considerable degree of satisfaction out of sucking and putting things in his mouth even when not hungry. Through the interaction of these various factors, there gradually comes about a strong interrelation between oral activity, the satisfaction of hunger, the receiving of affection, and the dependence upon outside agencies personified by the mother. This earliest stage of psychological development is characterized by the term *Oral Phase*.

During this phase in the development of the infant, there is reason to believe and evidence to support the theory that the infant looks upon himself as a sort of major god, the center of the universe, who has only to wish or need to have his wishes and needs granted. He is in his own eyes omnipotent. And why would he not be? When he is hungry he is fed, when he is wet he is changed, and when he is irritable he is petted and soothed. In short, he is



presented with evidence many times daily that he has only to wish to have his desires granted. But beginning with minor delays in being fed and consequent need for the recognition of objects in the environment other than himself, his greater perceptive capabilities and more extensive range of activities tend to reinforce and develop the psychological differentiation between himself and the environment. With the increasing maturation of his central nervous system he begins to crawl and walk to talk and to understand simple language and with this increase in his abilities it becomes necessary for society to impose restrictions on his activities and conduct both for his own safety and for the peace of others. Society in this case is in an usually personified by his mother and the most repetitive restriction placed upon him at this stage is usually that of bowel training. Not only must he learn to refrain from defecating whenever he so desires but also he is required to defecate at specified times and places. He soon learns that compliance with these wishes of the parents leads to approval and affection whereas failure leads to disapproval and the withholding of affection. Again he has begun to find and form an equation between his psychological needs and an organ function. It is common knowledge to all parents that bowel training seldom proceeds smoothly and that there is regression with physical stress such as illness, or psychological stresses such as jealousy or lack of attention. This phase of development is characterized by the psychoanalytic term *Anal Phase*. It must be added that the rich innervation of the rectum and anus tend to make the retention and expulsion of feces a pleasurable activity to the youngster, and he in turn unconsciously relates this pleasure to his bowel training and to the approval or disapproval of his parents. This discussion must not be construed as meaning that bowel training is the only psychological factor at work during this period of development; there are many others such as sibling rivalry, restriction of activities, testing of capabilities, jealousies and various other frustrations and demands. All of these factors obviously vary tremendously from individual to individual and the impact of them upon the child is equally varied both quantitatively and qualitatively. These variable factors are of importance in the development of the individual primarily because they constitute a threat to his goal, the undivided and exclusive possession of the attention and affection of his mother. Because of the close relationship usually within a family, the chief rivals for the affection of the mother are father and the siblings. This rivalry situation begins during the anal phase and continues during the succeeding phases.

As the child's control of his bowel activities increases, the importance of these activities as a mode of gaining attention and affection from the mother increases. It is usual for the child's urinary control to lag behind the control of the bowel; this and other factors tend to focus the interest of the child on the urinary processes and then demonstrable organ of function, the external genitalia. With this shift in interest to the external genitalia, the pleasurable potentialities of these organs are usually discovered. This early genital activity is the forerunner of later sexual activity but is still essentially autoerotic in nature. By autoerotic it is meant that the aim and object of this

pleasurable activity are contained in the child's own body. There is no external object for this primitive sexual activity. This phase of development is called the *Phallic Phase*.

Throughout the phallic phase there is an increase in awareness and exploration of its surroundings by the child. Rivalries become more intense and the demands for attention from the parent of the opposite sex become more compelling. The rivalries are directed towards sibling and towards the parent of the same sex and they have as their goal the total possession of the attention and affection of first the mother and then the parent of the opposite sex. Since these demands are strong and since the rival parent is to the child a tremendously powerful figure the psychological conflict engendered is one of considerable strength. In the average individual this conflict is usually resolved by means of identification with the parent of the same sex. Thus the child gains its goal by proxy as it were, and avoids the fantasied threat of punishment by becoming like its former parental rival. These complex situations are described in psychoanalytic terms as the Oedipus and Castration conflicts and they are believed by many psychiatrists to be the major constellations in the unconscious forces later giving rise to the psychoneuroses. They may be of singular importance in some of the psychosomatic disorders which appear as the individual grows older. This the *Genital Phase*, goes through a relatively long latent period during which sexual activity is at a minimum and continues until endocrinological functions produce the morphological changes of puberty at which time the psychosexual activity once more increases.

As the child grows older he becomes more and more active and the scope and number of his social contacts increase tremendously through the phallic and genital phases of his development. All through this period there is an ever increasing series of interests such as friends, school, sports, explorations of the manifold complexities of the world and people about him. Not only is there an acquisition of apparently new methods of reaction and new types of behavior but also there is the resolution and repression of emotions, conflicts and behavior patterns of earlier years. The successful resolution of these earlier conflicts and emotions is achieved primarily through the mechanism of sublimation that is the substitution of socially acceptable outlets for the more primitive and infantile drives which become socially unacceptable as the child grows older. However it must be made entirely clear that this process of resolution is almost never complete in any individual and the residual primitive and infantile drives and conflicts vary from person to person and range from a minor and relatively inconsequential proportion in some to the tremendously powerful and incapacitating conflicts in the psychotic. It is important to note that these infantile conflicts may never reach the level of conscious recognition by the individual and if they do they become repressed again into the unconscious. There they do not become inactive, instead they continue their disturbing and unacceptable activity manifesting themselves in pathological psychological and physiological symptoms recognizable anxiety or character or behavior disorders or eccentricities.

Whenever the basic needs and drives of the individual are opposed by the dictates of reality and the individual is prevented from fulfilling these wishes in a manner satisfactory to himself a conflictual situation is established in psychological terms this situation is called a conflict. The inevitable by product of a conflictual situation is anxiety. Originally in the life of the child this reaction is one of fear that is the recollection of a past experience in which the attempt to gratify an impulse or wish has led to painful results to the child. Primarily, the source of these painful experiences is external and frequently parental and we recognize the emotion of fear with its physiological concomitants as the resultant of a remembered or self evident external situation of a threatening nature. Anxiety is internalized fear. It is fear produced by inadequate or inappropriate stimuli it is usually proportionate to the stimulus both in intensity and duration and most importantly it does not lead to an appropriate adaptive solution. In the process of the conversion of fear into anxiety the memory of painful consequences becomes detached from the external situation and becomes psychologically related to the drives or wishes which led initially to the painful experience. Thus when ever that particular wish comes into play anxiety is activated. With the passage of time and as the result of past experience, an attempt is made by the individual to inhibit the enactment of this wish which leads to pain. This inhibiting process is given the psychological term repression. As has been previously indicated this preventive mechanism is seldom successful and the forbidden drive must be discharged in a substitutive way such as through symptoms sublimation etc. If it is not substitutively discharged with its physiological accompaniments the feeling of anxiety is experienced by the individual.

It is probable that the concept of the unconscious is the most important single step in the understanding of the formation of the manifold and complex symptoms with which the individual may be beset. In simple language the unconscious is that portion of the human mind which cannot be brought into direct awareness by ordinary means. It must not be considered as a circumscribed portion of the brain or body it is rather a conglomerate mixture of forces repressed memories experiences and fantasies which maintain a constant although variable interplay with each other and with those elements which are not unconscious. It is within the unconscious that much of the conflict between the basic drives of the individual the demands of reality and the dictates of society take place. On most occasions the acting out of these basic drives is not allowed by society or reality and they are dimmed back but the demands do not cease and as a consequence anxiety arises when they are in danger of becoming conscious. In order to protect himself against this anxiety and frustration the individual keeps the conflict repressed in the unconscious. For example when the young child wants a toy with which another youngster is playing he will demand it and if it is not immediately forthcoming will not hesitate to kick and bite to get the toy. As he grows older he soon begins to learn that such actions not only produce retaliation from the other child but also and more importantly lead to anger punishment and loss of affection from the all important parents. Therefore he

pleasurable activity are contained in the child's own body. There is no external object for this primitive sexual activity. This phase of development is called the *Phallic Phase*.

Throughout the phallic phase there is an increase in awareness and exploration of its surroundings by the child. Rivalries become more intense and the demands for attention from the parent of the opposite sex become more compelling. The rivalries are directed towards sibling and towards the parent of the same sex and they have as their goal the total possession of the attention and affection of first the mother and then the parent of the opposite sex. Since these demands are strong and since the rival parent is to the child a tremendously powerful figure, the psychological conflict engendered is one of considerable strength. In the average individual, this conflict is usually resolved by means of an identification with the parent of the same sex. Thus the child gains its goal by proxy as it were and avoids the fantasied threat of punishment by becoming like its former parental rival. These complex situations are described in psychoanalytic terms as the Oedipus and Castration conflicts and they are believed by many psychiatrists to be the major constellations in the unconscious forces later giving rise to the psychoneuroses. They may be of singular importance in some of the psychosomatic disorders which appear as the individual grows older. Thus the *Genital Phase* goes through a relatively long latent period during which sexual activity is at a minimum and continues until endocrinological functions produce the morphological changes of puberty at which time the psychosexual activity once more increases.

As the child grows older he becomes more and more active and the scope and number of his social contacts increase tremendously through the phallic and genital phases of his development. All through this period there is an ever increasing series of interests such as friends, school, sports, explorations of the manifold complexities of the world and people about him. Not only is there an acquisition of apparently new methods of reaction and new types of behavior but also there is the resolution and repression of emotions, conflicts and behavior patterns of earlier years. The successful resolution of these earlier conflicts and emotions is achieved primarily through the mechanism of sublimation that is the substitution of socially acceptable for the more primitive and infantile drives which become socially unacceptable as the child grows older. However it must be made entirely clear that this process of resolution is almost never complete in any individual and the residual primitive and infantile drives and conflicts vary from person to person and range from a minor and relatively inconsequential proportion in some to the tremendously powerful and unprejudiced conflicts in the psychotic. It is important to note that these infantile conflicts may never reach the level of conscious recognition by the individual and if they do they become repressed again into the unconscious. There they do not become inactive instead they continue their disturbing and unacceptable activity manifesting themselves in pathological psychological and physiological symptoms recognizable anxiety or character or behavior disorders or eccentricities.

believe that these activities are centered primarily in the frontal lobes. It is further probable that the central and controlling areas concerned with the peripheral physiological manifestations of the various emotions of a primitive variety are located in and near the hypothalamic area. Although accurate details are lacking, it is reasonable to assume that the cortex controls by inhibition or excitation the range and degree of activity of these hypothalamic centers. From the standpoint of the physiological responses to the various emotions it is evident from experiment and observation that the autonomic nervous system constitutes the major peripheral neuronal network in this chain. Through the autonomic system it is possible to affect all of the organ systems of the body. The chain of events is then that in emotion acting through the corticohypothalamic neuronal net and from thence through the autonomic system may influence any portion or organ system of the body. The body may be further influenced of course through voluntary and involuntary activity of the skeletal muscles under the control of the cerebral cortex.

Thus the mechanisms involved in psychosomatic disorders may be considered as divisible into three major spheres of activity: the corticohypothalamic or emotional sphere; the hypothalamic autonomic or neurohumoral mediating mechanism; and the local pathologic disturbance which consists of alteration in function or tissue or both. These considerations are important and also convenient diagnostically, therapeutically, and for the purpose of lucid description. It is not possible nor is it reasonable in discussion to separate the autonomic functions from the endocrinological and metabolic functions since they are so intimately and inextricably related they are thus subsumed under the term neurohumoral.

There is much evidence of both clinical and experimental nature to establish the conditioned reflex as an important factor in the development and continuation of psychophysiological functions. One has only to think of the salivation and gastric hypermotility when the hungry man is presented with the sight, smell, or thought of food to exemplify this thesis. It is probable that this complex interrelation plays an important role not only in the establishment of the normal psychophysiological reactions but also in the pathological psychosomatic mechanisms as well. Moreover it may be intimately involved in the problem of organ choice.

### ORGAN CHOICE

Perhaps the most vexing question in the whole field of psychosomatic medicine at the present time is that of organ choice. Why does one individual who is attempting to rid himself of anxiety by means of symptom formation develop cardiac manifestations whereas another individual manifests gastric symptoms? This is indeed a difficult question and it must be plainly stated here that we lack the necessary knowledge to formulate definitive and comprehensive answers to this question at the present time. We can present reasonable approximations with some assurance and in this we are rather like the man who is staring through binoculars at distant hills on

must learn to suppress (i.e. conscious subjugation) these antisocial wishes and before long this constant suppression leads by complex unconscious mechanisms to the complete repression of such wishes and regressive drives. Because these basic drives are not inactivated by being made unconscious the child must find some compromise solution. If he does not, intolerable anxiety develops. This compromise may take the form of partially releasing this aggressive drive by means of sports or some similar substitutive activity, or he may express his anger by a regression to a more infantile form of behavior or he may develop symptoms of a predominantly psychological character (e.g. conversion phobias compulsions, etc.), or physiological epiphenomena of psychogenic origin such as diarrhea, tachycardia, ticmor, etc. These physiological disturbances may or may not lead to tissue alteration. It is one of the inexorable laws of human life that some outlet must be found for this drummed up anxiety.

While most of the previous discussion has been devoted to the psychological development of the child and his conflicts it is not necessary to assume that these infantile conflicts are the sole and unsupported source of the symptoms and disturbances which appear later in life. It is unquestionable that the process of living inevitably leads to conflicts, disappointments, fears, and frustrations. These later conflicts may be entirely realistic and productive of anxiety such as the fear of death while in combat or they may gain power and become dangerous to the individual primarily by reinforcing or combining with the already existing conflicts of an infantile nature. It must be added that this latter combination of conscious and unconscious conflicts is by far the most common in present day living, although this opinion is debated by some schools of psychiatry. Whatever the source or age of the conflict the same psychodynamic processes are believed to operate and be valid.

In this greatly simplified discussion of psychological and psychiatric principles it becomes evident that each individual has his own characteristic set of reactions that the dictates of society and reality impose demands upon the individual which are often contrary to his basic wishes and drives and that these conflicting forces result in repression and the formation of unconscious conflicts which are laden with anxiety. We have further seen that in an effort to evade or eliminate this anxiety the individual is forced to develop some compromise solution and that this leads either to some acceptable substitutive activity or to symptom formation. Without going into detail it can be stated that this symptom formation is a neurotic solution and as such is never a satisfactory or entirely effective compromise. It is thus self-perpetuating although the manifest form of it (the symptom) may change with time. The question now arises as to how and through what mechanisms can these emotions influence the physiological functions of the body?

### PSYCHOPHYSIOLOGICAL MECHANISMS

It is entirely probable that the complex phenomena of thought and memory take place in the cerebral hemispheres mainly in the cortex and although such manifestations are probably diffuse there is evidence to support the be-

but that these activities are centered primarily in the frontal lobes. It is further probable that the central and controlling areas concerned with the peripheral physiological manifestations of the various emotions of a primitive variety are located in and near the hypothalamic area. Although accurate details are lacking, it is reasonable to assume that the cortex controls by inhibition or excitation the range and degree of activity of these hypothalamic centers. From the standpoint of the physiological responses to the various emotions it is evident from experiment and observation that the autonomic nervous system constitutes the major peripheral neuronal network in this chain. Through the autonomic system it is possible to affect all of the organ systems of the body. The chain of events is then that an emotion acting through the corticohypothalamic neuronal net and from thence through the autonomic system may influence any portion or organ system of the body. The body may be further influenced of course through voluntary and involuntary activity of the skeletal muscles under the control of the cerebral cortex.

Thus the mechanisms involved in psychosomatic disorders may be considered as divisible into three major spheres of activity: the corticohypothalamic or emotional sphere, the hypothalamic autonomic or neurohumoral mediating mechanism, and the local pathological disturbance which consists of alteration in function or tissue or both. These considerations are important and also convenient diagnostically, therapeutically, and for the purpose of lucid description. It is not possible nor is it reasonable in discussion to separate the autonomic functions from the endocrinological and metabolic functions since they are so intimately and inextricably related they are thus subsumed under the term neurohumoral.

There is much evidence of both clinical and experimental nature to establish the conditioned reflex as an important factor in the development and continuation of psychophysiological functions. One has only to think of the salivation and gastric hypermotility when the hungry man is presented with the sight, smell, or thought of food to exemplify this thesis. It is probable that this complex interrelation plays an important role not only in the establishment of the normal psychophysiological reactions but also in the pathological psychosomatic mechanisms as well. Moreover it may be intimately involved in the problem of organ choice.

### ORGAN CHOICE

Perhaps the most vexing question in the whole field of psychosomatic medicine at the present time is that of organ choice. Why does one individual who is attempting to rid himself of anxiety by means of symptom formation develop cardiac manifestations while another individual manifests gastric symptoms? This is indeed a difficult question and it must be plainly stated here that we lack the necessary knowledge to formulate definitive and comprehensive answers to this question at the present time. We can present reasonable approximations with some assurance and in this we are rather like the man who is staring through binoculars at distant hills on

a foggy day. He can delineate the main mill masses with certainty, but because of the fog he catches only an occasional glimpse of the finer details. At present it is not possible to present any integrated and holistic formulation of the determinants of origin choice but some of the probable factors involved can be listed.

**Hereditary and Congenital Factors**—It is evident that hereditary and congenital influences may encumber the individual with disabilities such as a malformed heart, an increased protein sensitivity, etc. These defective organs and functions will not only be predisposed to further trouble under the stresses of life but they may also become the focus for physiological disturbances of psychogenic origin.

**Accidental Factors**—The factor of chance may play a major role as a determinant. For example, an accidental injury or infection during the course of an intense emotional disturbance may tend to become the focal point to which these pathogenic psychological forces become related. Thus these psychological factors may increase the severity of the symptoms, prolong their duration or cause a return of similar symptoms and disorders during a later period of anxiety.

**Social Environment**—This rather inclusive phrase refers particularly to the family group and culture in which the individual lives. In many so-called familial diseases there is a tendency for the physician to confuse hereditary transmission of the disorder and the emulation of some parental disorder by the child. There is an almost universal tendency on the part of the child to ape the mannerisms and characteristics of one of the parents, usually the parent of the same sex. This proclivity on the part of the child applies to the pathologic characteristics of the parent as well as to the desirable traits and patterns. The child wants to be like the parent in every respect. This attempt to be like the parent has its origins largely in the unconscious and its complex dynamics are described by the term identification. Examples of this process may often be seen in families which have a high incidence of some particular dysfunction such as headaches, ingestion, dysmenorrhea, etc. The process of identification may be of paramount importance in selecting the mode of discharge for anxiety and thus in time may lead to a constant pattern of psychosomatic dysfunction for a certain origin. "It runs in the family" does not necessarily mean that the disorder is hereditary. A similar mechanism may permit the individual to identify with a group with which he is closely associated and thus we may see an apparent epidemic of a specific psychosomatic disorder in a closely knit group such as a group of soldiers or in racial and cultural groups not because of racial determinants but because of the psychological resultants of social environmental stresses.

**Iatrogenic Factors**—Some symptoms or disabilities may be initiated wholly or in part by the physician. For example, an individual may seek consultation by reason of minor precordial discomfort and palpitation which are of psychogenic origin and he may be told by the uncertain or unskilled physician that he may have heart trouble or that he has a weak heart. This unfortunate and authoritative confirmation of the patient's fears may



lead him to consider himself as a chronic invalid and thus cause him to restrict his social and economic activities accordingly. In certain instances this may lead through various complex psychophysiological mechanisms to eventual tissue pathology and death.

**Symbolic Equivalents**—Among psychodynamic concepts that of affect equivalent or symbolic equivalent is the most important of the psychodynamic mechanisms which are directly related to psychosomatic medicine. In order to clarify this concept it is necessary to recall that in infancy there is an almost complete equivalence between certain psychological and physiological reactions recompensating hunger. The satisfaction of both of these depends upon the mother and they are so closely identified in the mind of the infant as to be almost indistinguishable. If conflicts which involve this relationship are established and repressed in infancy then at a later date situations which threaten the security of the unconsciously overdependent person may be related to by means of gastric hypermotility, mucosal engorgement and hyperacidity. This almost literal hunger for affection and security when long continued may establish the gastric dysfunction which is the necessary precursor to the development of peptic ulcer. Many other similar psychophysiological relationships exist and will be discussed later.

**Behavioral Factors**—It is common knowledge that neurotic conflicts may lead to minor or major deviations from the usually accepted norms of behavior. It is not common knowledge however that these neurotically originated behavioral patterns may be the all important factor in the repeated exposure to certain diseases and injuries. For example an individual with powerful unconscious conflicts of a sexual nature may be driven to repeated and indiscriminate sexual relations and he may thus contract a new gonorrheal infection almost as soon as he has been cured of the previous attack. In other individuals neurotic conflicts may lead them repeatedly into dangerous situations and thus predispose to a high degree of accident proneness. Variations of this dynamic mechanism could be multiplied almost indefinitely and involve almost all bodily systems.

We have seen that transient emotional stimuli can produce important physiological changes of a temporary nature and that the unconscious conflicts may act as persistent and insatiable stimuli. It is this quality of persistence and insatiability on the part of unconscious conflicts even in the face of denial by reality which leads to their importance in the understanding of psychosomatic medicine for when they become related to physiological dysfunction as they frequently do then continuous although variable excitation of an abnormal physiological function may lead to permanent cellular and tissue alteration. This relationship may be schematically illustrated as follows:

Continuous unconscious conflict	Continuous physiologic dysfunction
Reversible cellular change	Irreversible cellular change

It must be noted further that any unconscious conflict may have its power as a stimulus strongly reinforced both by other unconscious conflicts and by current conscious conflicts and situations.

## GENERAL CONSIDERATION OF THERAPY

It is desirable here to re-emphasize the general thesis implied and expressed above that all disease has a psychosomatic component. It must be recognized that the role of the psychological factors with which we are concerned in this chapter and their relationship to the biologic and environmental factors involved in disease is not a simple one. The psychological factors may be of primary importance in the etiology or they may exist as concomitants or they may appear as sequelae of any disease. Not infrequently they must be given consideration in all three aspects. It is of the utmost importance not only that the psychological factors be recognized but also that they be carefully evaluated in their relationship to the biologic and environmental forces active in each individual patient. Not only must this evaluation be carried out during the initial survey of the patient but also it must be followed by careful and repeated re-evaluations during the stages of active therapy and convalescence. It is an inherent property of the living animal that the dynamic balance of the biological, psychological and environmental forces is constantly shifting, and particularly is this true throughout the full course of disease.

In general the therapeutic aspects of psychosomatic medicine may be subsumed under three main headings:

- 1 Biological Measures—e.g., pharmacological, surgical and general supportive therapies
- 2 Environmental Measures—e.g., public health aspects
- 3 Psychological Measures—e.g., psychotherapy

All three of these therapies are interdependent to a certain degree but since the first two are discussed elsewhere in the book we shall concern ourselves primarily with the third category.

It must be stated unequivocally that the first requisite of adequate psychological evaluation of the patient and subsequent effective therapy is a lucid understanding of the major principles of personality structure and basic psychodynamics. Just as effective biological therapy must be based upon a sound knowledge of physiology and pathology, so must appropriate psychotherapy be founded upon a clear conception of the basic principles of psychodynamics and personality structures. It is unfortunately true that the knowledge of human psychology has not yet progressed to a point which permits a universal acceptance of a single schematization; nevertheless there is a sufficient body of organized data to justify a wide acceptance of basic principles. Psychiatry like all other branches of medicine is undergoing a constant growth and revision.

In psychosomatic medicine as in all other branches of medicine where psychological factors are of concern, the factors of primary psychotherapeutic concern are three: the attitudes of the patient in relation to his disease, the relationship of patient and physician and the attitudes of the physician. An exhaustive discussion of these three considerations is far beyond the scope of this chapter and for detailed information about them the reader is referred to standard textbooks of psychiatry and psychotherapy, some of which are listed in the bibliography. In spite of this limitation it is of importance to indicate some of the more important features.

**Attitude of the Patient**—In his approach to the physician the patient presents not only certain biological and symptomatological manifestations but also certain attitudes and feelings which may be of extreme importance in the proper evaluation and treatment of his disorder. These feelings and attitudes are for the most part not apparent to the patient himself and where they are he considers them to be either unrelated to the disorder or at the most a direct result of it. Since these feelings are manifestations of his personality structure which is in turn a product of memories and conflicts which are largely unconscious this unawareness on the part of the patient should not be occasion for surprise. In general the patient is not aware of the existence of these painful repressed memories and even when he is dimly aware of their existence he cannot comprehend the relationship of these conflicts to his symptoms. As stated previously these unconscious conflicts with or without reinforcement from reality situations may be etiological in respect to his symptoms. In other instances these conflicts may produce concomitant psychological disorders which materially interfere with proper treatment. For example the individual with a marked resentment of authority arising out of strong unconscious hostility towards the father may refuse to accept badly needed treatment because of the authoritarian role of the physician. Even where realistic fears arise in relation to a known disease they may be powerfully intensified through becoming related to unconscious conflicts and the same conflict may be at once etiological for the disorder and the source of the overcharging of the realistic fear.

Usually the patient looks upon his symptom or disease as a matter of chance misfortune or a visitation of Providence. He does not consider that his psychological activities could have any real part in the process and he may actively resist or resent any implication that his symptoms are essentially psychogenic in origin. This is due in part to our present day social attitudes in which neurotic disorders are mistakenly considered as being imaginary or somehow shameful but more importantly the patient is psychologically incapable of accepting such an explanation directly because it disturbs his own defensive mechanisms. It must be remembered that these unconscious conflicts were originally repressed because they were painful to the individual and that any attempt to bring them into consciousness meets with immediate and powerful resistances. Furthermore since the repression of the conflict did not remove the anxiety it was necessary for the individual to find some outlet for the anxiety and in the psychosomatic disorders the outlet chosen even though relatively ineffectual and potentially dangerous is a physiological disturbance or symptom. The resistances stirred up in the individual can take the form of evident anxiety, disbelief, anger or an intensification of the symptom to mention but a few.

To make more explicit one of the implications contained above the patient is not only incapable of bringing unconscious material directly into consciousness but also injudicious attempts on the part of the physician to make him do so or to make him understand his unconscious conflicts by confronting him directly with them may lead to serious psychological and physiological harm to the patient.

**Relationship of Patient and Physician**—It is safe to state that no patient voluntarily consults a physician with a completely unbiased attitude. Even before he comes to the doctor he has formed certain concepts and feelings about this authoritarian figure he is about to consult. He believes consciously that he has chosen that particular therapist because of things he knows or has heard about him and his abilities. While these reality judgments exist as such they are largely built upon the scaffold of the unconscious feelings and attitudes formed in childhood and augmented, decreased, or varied since their inception. These all important unconscious attitudes of childhood are largely formulated upon his relationships and feelings towards his parents and he brings to and transfers upon the physician this complex mixture of dependence, love, hate, rivalry or fear which characterized his earlier relationships with his family and particularly his parents. This means that the patient approaches the physician in the relation of child to parent and the wise physician unconsciously or consciously realizes this and makes use of it in his treatment of the patient. It must be emphasized that this relationship and transference of unconscious emotions of childhood origin onto the person of the doctor is an action of which the patient is entirely unaware and which because of its unconscious character he cannot possibly verbalize or express directly other than in terms of feeling and behavior. Every physician of experience has seen many examples of apparently unexplainable overdependence, sudden resistance, adoration or strong hostility develop during his treatment of the patient. These apparently inexplicable attitudes are easily understood if the physician takes cognizance of the universal and powerful character of the transference relationship. In simple terms, *transference* means the unconscious investment of the physician with the emotions derived from the early familial relationship which persist in the unconscious of the patient. This transference relationship of patient and physician is not a static one throughout the whole course of the treatment it is constantly changing with now one emotion dominant and then another. The skilled physician may intuitively sense these changes and alter his attitudes accordingly but the sure handling of this very difficult problem must depend upon a clear understanding of psychodynamic mechanisms if it is to be uniformly effective. The correct interpretation of transference reactions and the proper utilization of this knowledge is by far the most difficult problem in the whole field of psychotherapy. It can be added that many of the temporary improvements in the condition of the patient and subsequent therapeutic failure of the same treatment are in reality merely manifestations of the psychological changes engendered by the transference relationship.

The relationship between the patient and physician is not a one-sided affair. It must be evident that since the patient invests the physician with the powerful unconscious feelings transferred from the parents, the role played by the physician in the feelings of the patient cannot be an emotionally neutral one.

**Attitude of the Physician**—If the foregoing statements are correct and there is excellent evidence that they are it becomes axiomatic that the unconscious and conscious attitudes of the physician play an important role in

the patient-physician relationship. Just as most of the patient's emotional responses to the doctor are based upon his unconscious experiences and conflicts so are the physician's attitudes and reactions toward the patient derived from his own unconscious emotional constellations. Thus the needs and demands of the patient expressed in his attitude and behavior may produce powerful reactions in the therapist and materially alter his feelings and behavior towards the patient. Often this alteration in attitude and behavior towards the patient may go unrecognized by the physician because the changes are brought about by impact on conflicts which are entirely unconscious. Many errors in therapy are brought about by this mechanism, the countertransference. For example, the demands of the aggressive patient upon the therapist may lead the physician to hasten his examination in order to be rid of the annoying patient and thus cause him to overlook some rather obvious pathology which he would not have missed had he not hastened his examination. One of the commonest errors in medicine today is the repetitive search for organic causes of a symptom or disorder even though the physician is reasonably sure that the origin of the symptom is psychological. This procedure usually stems from the physician's own insecurity. He is fearful of the censure of his colleagues and patient if he should overlook some pathology and yet he will cheerfully pass by ten times as many neurotic disturbances whose consequences may be equally if not more serious to the patient. Or he may avoid an obvious diagnosis of a psychogenic disorder in order to avoid the loss of self-esteem consequent upon the admission that he does not know how to treat it. Many other examples of the effect of the physician's unconscious and conscious attitudes upon the therapy of the patient could be given but these few should indicate the importance of the physician's attitude in the realm of therapeutics.

## PSYCHOTHERAPY

A discussion of the actual techniques of psychotherapy is beyond the province of this book, however, some of the more important features of such therapy may be considered under two descriptive headings which cover almost all of the field of psychotherapy, namely, expressive and suppressive therapy. It is implicit in any form of psychotherapy that the phenomena of transference and countertransference discussed above are an integral and important part of such treatment.

**Expressive Psychotherapy**—The primary aim of this form of treatment is to relieve the patient's symptoms and anxiety by means of breaking through his defenses (*resistances*) and discharging the inappropriate and excessive emotions bound up in the unconscious pathogenic memories and drives. It is thus aimed at the relief of symptoms by the removal of their causes. Because of the fact that the underlying conflicts and resistances lie mainly in the realm of the unconscious and preconscious and because of the patient's inability to tolerate anxiety in other than minimal amounts and for other technical reasons, this process must be carried out in a carefully controlled step by step fashion. In general, expressive psychotherapy makes use of exploration, abreaction, interpretation, transference reactions, free association and related devices, but most subvarieties of this therapy do not exclude the con-

temporary use of some supportive measures such as suggestion, re education, etc. Expressive or deep psychotherapy is time consuming and technically complex and for this reason must remain largely a tool for the specialist in psychiatry.

**Suppressive Psychotherapy**—Suppressive psychotherapy is often labeled supportive or superficial psychotherapy. The latter term is misleading because the proper practice of such therapy not only must be based upon a thorough knowledge of psychodynamics but also may have profound effects upon the patient. The results obtained through suppressive psychotherapy are frequently impressive and indeed it is not infrequently the method of choice in treatment when reality factors such as time, availability of therapy, psychological accessibility of the patient etc., govern the decision. However the aims of suppressive psychotherapy are diametrically opposed to those of expressive therapy. Whereas the latter tries to remove the underlying causes of the conflicts the former (suppressive) therapy aims at restoring the defenses and adaptive mechanisms of the patient so that he may suppress the causes of the symptom and regain his former controlled status. In particular the therapist may attempt to aid the reintegration and strengthening of the patient's defenses by means of such methods as reassurance suggestion counseling re education inspiration alteration of noxious environmental factors increasing the number and type of substitutive outlets for anxiety, etc. In his endeavors the physician may and should use the powerful forces of the transference situation to increase the efficiency of the measures chosen. It is a melancholy fact however that these methods are used far too frequently without any clear concept of psychodynamics in general or knowledge of the patient's own background and dynamics in particular. Such misguided use of psychological methods in treatment will be of no benefit to the patient at best and may lead to a serious intensification of the morbid psychological and physiological processes.

**Practical Aspects of Therapy**—In psychosomatic medicine the general concepts of psychotherapy given in brief above have certain important practical applications. Perhaps the foremost of these is that psychotherapy on a nonverbal level in the transference relationship begins with or before the initial interview of the patient and continues throughout the entire therapeutic relationship. Whenever possible it is highly desirable for the physician to begin his psychological assessment of the patient concurrently with the organic diagnostic procedure. This can be done without great difficulty by giving careful attention to the degree and type of manifest anxiety behavior attitude of the patient towards his disorder and the physician the chain of verbal associations etc. It may be and frequently is advisable to explore superficially the psychological background and the conscious fears and problems of the patient at the initial interview. This must be done with some caution in order to avoid an undue mobilization of anxiety; it is wise to avoid a too deep or persistent direct exploration of suspected areas of conflict even though they appear to be superficial. The study of the patient's problems defenses, and reactions must proceed *pari passu* with the organic investigation.

tion for the diagnosis of psychopathology is arrived at by positive measures and not by exclusion of organic disease.

When there is a reasonable degree of certainty in the mind of the physician that the symptoms do not arise from organic pathology the patient must be immediately and authoritatively reassured about the absence of related organic pathology. It must be made explicitly clear to the patient at the same time that emotional conflicts or nervous tension can produce such symptoms as the patient complains of and that further exploration and treatment of a psychological nature will be necessary if the complaints are to be removed. At the present time it is often wise for the therapist to assure the patient that disorders of psychogenic origin are not 'imaginary' and the wise physician can profitably reinforce this view by illustrations from the patient's own experience e.g. blushing, tachycardia from fear, nausea and vomiting from disgust etc. The physician must resist the temptation and the entreaties of the patient to 'prescribe something' and above all he must resist the trap of prolonged and useless search for organic causation because of his own fears or insecurities. Many patients have been done nearly irreparable harm through a psychological fixation on a given symptom or disorder by means of such unnecessary examination and re-examination.

When tissue pathology has been demonstrated and where psychological mechanisms are present in an etiological concomitant or secondary role psychotherapy may be not only advisable but even imperative if alleviation or cure of the condition is to be expected. It is generally advisable that appropriate psychotherapy be implemented concurrently with such local or general biological measures as may be indicated. With combined therapy of this type it is absolutely necessary that the patient have a clear appreciation of the role of each of these measures in his treatment. The choice of methods of treatment both in biological and psychotherapy is a very difficult problem at times and the determination can never be made effectively except when based upon a secure knowledge of the biological, psychological and environmental factors which constitute the frame of reference of that particular patient.

### SYSTEMIC CONSIDERATIONS

In the discussion of the psychological factors related to the diseases of specific organs symptoms and causes of a purely organic type will be omitted since they are considered elsewhere in the book. Although psychological factors will be emphasized particularly in their etiological significance there is no intention to indicate that emotional factors are the sole agents of importance. Even where there is some reason to believe that a disorder is of psychogenic origin organic mechanisms must furnish the intermediary channels of action and at times tissue alteration with resultant organic dysfunction may be the end result. Moreover when dysfunction is of primary organic origin unrelated emotional conflicts may be intensified and become related to the disorder complicating the symptomatic reactions and increasing the degree of disability. In no situation can we afford to neglect consideration of the disease from the combined viewpoint of organic, psychological and environmental factors.

## RESPIRATORY SYSTEM

It is a matter of easy observation and common knowledge that the function of respiration is influenced not only by the normal physicochemical methods of control, but by emotional reactions as well. Each of us is familiar with the held breath of suspense, the rapid breathing of excitement and fear, the irregular sobbing of grief and the deep sighing of perplexity and tension. All of these variations are normal phenomena when they do not exceed reasonable limits of intensity or duration. On the other hand, when the exciting stimuli, whether they be of an organic or emotional origin or a combination of both, are of an abnormal intensity or continue to act, striking symptoms and profound bodily changes may ensue. We are concerned here primarily with those of psychogenic origin, the organic pathophysiological phenomena are discussed elsewhere in the book. Although acute transient emotional disturbances may produce symptoms and disorders which bring the patient to the physician, it is far more common to find that the emotional conflicts which cause the symptoms are partially or deeply buried in the unconscious and are chronic in nature. The mechanisms involved in this process have been discussed in a general way in the preceding sections. Among the common symptoms which may be partially or entirely psychogenic in origin are the following:

**Dysrhythmia**—Minor variations in the amplitude and frequency of respiration are normal and are the means by which an optimum gas tension is maintained in the blood. Emotional stimuli may provoke and continue marked alteration in the rate, rhythm or amplitude of respiration (see pages 330 to 333). Among the commonest forms of such respiratory disturbances are intermittent deep sighing, shallow hyperpnea, apparent dyspnea and mild stidor. Many types of psychogenically originated dysrhythmias have been demonstrated on respiratory tracings by Mackays, Christie, Alexander and Saul and others. Usually these alterations are the direct result of anxiety; however, conversion compulsion or the like mechanisms may produce similar symptomatic results. The underlying psychodynamic mechanism can be determined only by a study of the individual case. A psychogenically originated dysrhythmia may exist as such or it may appear as a concomitant or sequela of an organic dysrhythmia.

**Hyperventilation**—This symptom is a common one during periods of anxiety and is usually present in a minor form. However, it may progress to the point of producing tetany, syncope or even convulsive manifestations in the susceptible individual.

**Cough**—One of the commonest symptoms in the field of medicine is that of cough. While it is obvious that persistent cough must lead to a thorough search for underlying organic pathology, it is far too often forgotten by the physician that psychogenic factors may increase the severity of the cough, continue it long after the original organic source of the cough has disappeared or even produce it without the existence of organic pathology. Some experimental evidence exists which seems to indicate that even in conditions where chronic cough is due to an initial organic pathology, such as tuberculosis,



psychotherapy may be of material benefit in lessening the severity of the cough. The persistence of a cough beyond a reasonable length of time after the disappearance of organic pathology always should lead to the suspicion that persistence of the cough is due to psychogenic rather than organic causes. This is particularly true when the cough is or becomes emetic in type. It is generally believed by most psychoanalysts that cough of psychogenic origin usually results from the individual's finding that he has introjected (ingested) some object which leads to a feeling of guilt and disgust. He is thus by means of the cough (or vomiting) trying to rid himself symbolically of this introjected object. There is much evidence in the literature to support these views.

**Dysphonia**—The various forms of dysphonia such as aphonia, hoarseness, whispering, and undue vocal fatigue are not uncommon manifestations of conversion hysteria.

**Asthma**—That the diverse entity of bronchial asthma represents a clear cut example of a psychosomatic disorder has already been discussed. Involved in the consideration of this disorder are the factors of sensitivity to allergens, the exposure to these allergens and certain psychological considerations. The coexistence of a specific sensitivity and the exposure to that allergen are not enough in themselves to explain the occurrence of asthma for it is well known that an individual sensitive to house dust for example may develop not asthma but urticaria, eczema, hay fever or an idiosyncratic edema instead. Furthermore, there is definite clinical evidence that some individuals suffering from asthma and sensitive to a specific allergen may be completely freed of their asthma by means of psychotherapy and yet retain sensitivity as measured by skin test to the same allergen. There is further evidence to the effect that an individual sensitive to a certain allergen may have an attack of asthma precipitated by an appropriate emotional stress in the complete absence of the specific allergen. It is thus evident that psychogenic factors must play an essential role in the production of asthma in many if not all individuals.

1. The attacks occur as a reaction to the danger of separation, real or fantasized from the mother. The place of the mother may be taken by some surrogate figure in the life situation of the individual. The therapist may come to represent such a figure to the patient during the course of treatment.

2. The attack is often a sort of equivalent of a repressed anxiety or rage. It is noteworthy that crying is rare in the asthmatic. The attacks tend to appear in its stead.

3. Situations which stimulate the fear of loss of the mother may be either a realistic threat or they may be a temptation usually sexual or aggressive in nature and one which the mother would disapprove that encourages the breakthrough of repressed impulses. Attacks were found to occur when the defenses against such impulses either broke down or were suddenly and severely threatened.

4. The task of mastering the fear of being left alone governs the patient's whole life.

5 There is a considerable variation in the character structure of the patients involved in these studies, but a lack of independence and a marked dependence upon the mother or some surrogate appeared to be common to all.

6 In most instances it will be found that the mother tended to be pathologically overprotective often in a reaction to her unconscious wish to reject the child.

Because of the multiple etiological factors involved in bronchial asthma it is evident that proper therapy will involve the determination of the implicated allergens, desensitization in many instances and adequate psychotherapy. While deep psychotherapy would be desirable for many of these cases it is obvious that economic and time factors will prevent the universal application of such measures. The so-called "superficial" psychotherapy will be of material benefit to many of them and should be directed towards the establishment of a strong positive transference so that the patient can have the maximum dependence on the therapist. Supportive measures may be of considerable use in attaining this end. As the patient gains confidence in the physician it has often been noted that there is a tendency for him to "confess" partially repressed conflictual material and that following such confessions there is usually a marked amelioration of the disorder at least for a time.

**Pulmonary Tuberculosis**—It must be stated at the outset that there is little reliable data on the psychosomatic aspects of pulmonary tuberculosis. On hypothetical grounds it appears to be entirely probable that the psychological factors such as prolonged hospitalization, separation from the family, chronic invalidism, etc. may have profound effects upon the course of the disease and upon the subsequent life of the patient. Whether or not psychogenic factors may be concerned in the etiology of this disorder remains to be determined.

Tuberculophobia is by no means rare and the failure to recognize this fear in a patient may lead to an almost irretrievable fixation of this belief. On the other hand prompt diagnosis and powerful reassurance may dissipate the belief in its early stages and thus avoid years of semi invalidism.

**Recurrent Upper Respiratory Infections**—There are many well documented instances of the cure of the tendency towards frequently recurring colds and similar infections. Such cases have usually been reported as occurring during or after psychotherapy for other conditions. Little is known of the mechanisms involved but it is now beyond the realm of speculation that psychosomatic processes may be profoundly involved in at least some cases of recurrent respiratory infection.

## CARDIOVASCULAR SYSTEM

During the last few decades the development of an increasing accuracy of diagnostic procedures has made it apparent that at least 50 per cent of the patients who consult physicians because of complaints which they believe to be due to the heart are found to have no demonstrable organic pathology of the cardiovascular system. Even when organic lesions can be proved approximately 30 per cent of the symptoms cannot be attributed to the organic pathology. The studies of Dunbar indicate that from 60 to 98 per cent of pa-

tients with various cardiac complaints or disorders have been exposed to cardiovascular disease or sudden death among friends or relatives whereas in control studies the incidence is less than 40 per cent. It is thus not surprising that any symptom which the patient believes to be due to the heart should be equated in his mind with visions of pain, invalidism or sudden death. These fears are reinforced daily by tales of friends and stories in the newspaper. Not only do these experiences increase the fear and anxiety of the individual with cardiac complaints but also they prepare a fertile field for the growth of symptoms of psychogenic origin.

As W. C. Munnicker points out no other organ is so intimately associated with the feelings of love and hate in our language as is the heart. While it is true that this body language is derived in part from primitive physiological misconceptions it is equally true that everyday experience demonstrates the alterations of rate, rhythm and force of the heartbeat which accompany strong emotions. In addition we see visible evidence of neurovascular changes and observe clinically the changes in blood pressure which accompany the emotions of fear, hate and love. It should not be surprising then that when such emotions are frequently experienced or become chronic through neurotic dynamics there may result in certain individuals symptomatic manifestations or pathophysiological phenomena which may lead eventually to tissue and structural alterations in the cardiovascular system. As in most psychosomatic disorders these psychophysiological reactions are mediated through neurohumoral mechanisms primarily the autonomic nervous system.

Numerous clinical psychiatric and psychoanalytic studies have indicated that the central psychological motif commonly associated with cardiovascular disorders is that of hostility and repression. Usually these impulses are closely integrated with unconscious sexual conflicts of a primitive nature. Not infrequently these unconscious sexual impulses directed towards one or the other parent lead to partially or totally repressed hostile wishes towards the opposite parent. In the unconscious these hostile wishes tend to be envisioned in terms of total destruction of the opponent and because of guilt reactions and the fear of retaliation such wishes tend to produce profound fears of death in certain individuals. Through psychodynamic processes such as identification the reactive mechanisms of the cardiovascular system become responsive to the stimulation of these emotional constellations of hostility.

Symptoms related to disorders of the heart due to organic lesions or due to psychophysiological manifestations may be considered under several main categories: (1) pain or discomfort in the precordial area; (2) dyspnea; (3) disorders of rhythm and tachycardia; (4) murmurs; and (5) others such as fatigue, giddiness, insomnia, etc. The pathophysiological manifestations of organic origin are discussed elsewhere in the book but almost all of the above mentioned symptoms either may be of psychogenic origin or may appear as psychological concomitants or sequelae of cardiac dysfunction.

**Pain or discomfort in the precordial area** is a common presenting complaint exhibited by the patient with a heart disorder of an organic or psycho

5 There is a considerable variation in the character structure of the patients involved in these studies, but a lack of independence and a marked dependence upon the mother or some surrogate appeared to be common to all.

6 In most instances it will be found that the mother tended to be pathologically overprotective often in a reaction to her unconscious wish to reject the child.

Because of the multiple etiological factors involved in bronchial asthma it is evident that proper therapy will involve the determination of the implicated allergens, desensitization in many instances, and adequate psychotherapy. While deep psychotherapy would be desirable for many of these cases it is obvious that economic and time factors will prevent the universal application of such measures. The so-called "superficial" psychotherapy will be of material benefit to many of them and should be directed towards the establishment of a strong positive transference so that the patient can have the maximum dependence on the therapist. Supportive measures may be of considerable use in attaining this end. As the patient gains confidence in the physician it has often been noted that there is a tendency for him to "confess" partially repressed conflictual material, and that following such confessions there is usually a marked improvement of the disorder at least for a time.

**Pulmonary Tuberculosis**—It must be stated at the outset that there is little reliable data on the psychosomatic aspects of pulmonary tuberculosis. On hypothetical grounds it appears to be entirely probable that the psychological factors such as prolonged hospitalization, separation from the family, chronic invalidism, etc., may have profound effects upon the course of the disease and upon the subsequent life of the patient. Whether or not psychogenic factors may be concerned in the etiology of this disorder remains to be determined.

Tuberclephobia is by no means rare and the failure to recognize this fear in a patient may lead to an almost irremediable fixation of this belief. On the other hand, prompt diagnosis and powerful reassurance may dissipate the belief in its early stages and thus avoid years of semi-invalidism.

**Recurrent Upper Respiratory Infections**—There are many well-documented instances of the cure of the tendency towards frequently recurring colds and similar infections. Such cases have usually been reported as occurring during or after psychotherapy for other conditions. Little is known of the mechanisms involved but it is now beyond the realm of speculation that psychosomatic processes may be profoundly involved in at least some cases of recurrent respiratory infection.

## CARDIOVASCULAR SYSTEM

During the last few decades the development of an increasing accuracy of diagnostic procedures has made it apparent that at least 50 per cent of the patients who consult physicians because of complaints which they believe to be due to the heart are found to have no demonstrable organic pathology of the cardiovascular system. Even when organic lesions can be proved approximately 30 per cent of the symptoms cannot be attributed to the organic pathology. The studies of Dunbar indicate that from 60 to 90 per cent of pa-

tients with various cardiac complaints or disorders have been exposed to cardiovascular disease or sudden death among friends or relatives whereas in control studies the incidence is less than 40 per cent. It is thus not surprising that any symptom which the patient believes to be due to the heart should be equated in his mind with visions of pain, myocardial infarction or sudden death. These fears are reinforced daily by tales of friends and stories in the newspaper. Not only do these experiences increase the fear and anxiety of the individual with cardiac complaints, but also they prepare a fertile field for the growth of symptoms of psychogenic origin.

As W. C. Menninger points out, no other organ is so intimately associated with the feelings of love and hate in our language as is the heart. While it is true that this body language is derived in part from primitive physiological misconceptions, it is equally true that everyday experience demonstrates the alterations of rate, rhythm and force of the heartbeats which accompany strong emotions. In addition, we see visible evidence of neurovascular changes and observe clinically the changes in blood pressure which accompany the emotions of fear, hate and love. It should not be surprising, then, that when such emotions are frequently experienced or become chronic through neurotic dynamics, there may result in certain individuals symptomatic manifestations or pathophysiological phenomena which may lead eventually to tissue and structural alterations in the cardiovascular system. As in most psychosomatic disorders, these psychophysiological reactions are mediated through neurohumoral mechanisms, primarily the autonomic nervous system.

Numerous clinical psychiatric and psychoanalytic studies have indicated that the central psychological motif commonly associated with cardiovascular disorders is that of hostility and aggression. Usually these impulses are closely integrated with unconscious sexual conflicts of a primitive nature. Not infrequently these unconscious sexual impulses directed towards one or the other parent lead to partially or totally repressed hostile wishes towards the opposite parent. In the unconscious these hostile wishes tend to be envisioned in terms of total destruction of the opponent, and because of guilt reactions and the fear of retribution such wishes tend to produce profound fears of death in certain individuals. Through psychodynamic processes such as identification, the reactive mechanisms of the cardiovascular system become responsive to the stimulation of these emotional constellations of hostility.

Symptoms related to disorders of the heart due to organic lesions or due to psychophysiological manifestations may be considered under several main categories: (1) pain or discomfort in the precordial area; (2) dyspnea; (3) disorders of rhythm and tachycardia; (4) murmurs; and (5) others such as fatigue, giddiness, insomnia, etc. The pathophysiological manifestations of organic origin are discussed elsewhere in the book, but almost all of the above mentioned symptoms either may be of psychogenic origin or may appear as psychologic concomitants or sequelae of cardiac dysfunction.

**Pain or discomfort in the precordial area** is a common presenting complaint exhibited by the patient with a heart disorder of an organic or psycho-

genic origin. The differential diagnosis usually does not present great difficulty when a careful history is taken. Pain of an organic origin is usually directly related to exertion, whereas pain of psychogenic origin is in most instances found to be either partially or totally unrelated to physical exertion and is in fact often found to occur only when the individual is at rest. Moreover the character and distribution of the pain described by the patient with a psychogenic disorder are most often atypical. He tends to locate the pain in the region where he believes that his heart lies, and there is seldom any radiation of the pain. Close questioning frequently reveals that the "pain" is in reality a sense of oppression or superficial hyperesthesia rather than of the type typical of angina pectoris, coronary occlusion, neuritis, etc. Of the utmost importance is the fact that proper investigation will disclose the neurotic background and experiences from which the symptoms have developed. In many individuals the strong reassurance as to the absence of organic disease will lead to the disappearance of the pain. When true anginal pain occurs it may become much more difficult to assess the part played by psychological factors for clinical and experimental evidence has demonstrated that alterations in the function of the coronary arteries may be produced by emotional stresses of a conscious or unconscious nature. Only careful psychiatric investigation can elicit these factors in the majority of such cases.

**Dyspnea** is an equally common complaint in cardiovascular disorders, and, as a symptom the assessment of its origin rests primarily upon its relation to exertion. In the absence of cardiac asthma when dyspnea is unrelated to physical effort it is highly probable that it springs from stimuli of a psychological nature rather than from organic cardiac pathology. Characteristically the disturbance of respiration will be found to consist of intermittent deep sighing breathing with complaints by the patient of an inability to get a full breath or of a feeling of pressure in the chest (see Fig. 333). Tachypnea and hyperventilation are seen at times as a neurotic cardiac complaint. In almost all cases the differential diagnosis between psychogenic and organic dyspnea can be made easily upon the basis of a careful history. Respiratory tracings may furnish excellent corroborative evidence in doubtful cases.

**Disorders of rhythm and tachycardia** are often the basis of complaints referred to the heart by patients with cardiac disorders of psychogenic origin. Whereas a transient tachycardia is the normal accompaniment of passing emotional stimulation such as fear, anger, and excitement the persistence of these emotions may lead to a chronic although variable state of tachycardia. It is usual to find such a condition in anxiety neurosis and neurocirculatory asthenia and it is probable that the underlying emotional conflicts acting through the autonomic system and sinoauricular node produce this tachycardia (see page 373). A more common source of subjective complaint is that of premature beat or extrasystole. This is usually experienced by the patient as a sense of skipped beat or palpitation and the sense of discomfort frequently reinforces the individual's belief that he is suffering from heart disease. In the absence of an organic lesion there is clinical and experimental evidence to indicate that emotional stimuli acting through the autonomic system may produce extrasystoles. Failure on the part of the physician to reassure the

patient is to the absence of organic heart disease or the injudicious use of medication "to decrease the irregularity" may serve to confirm the patient's fears of heart disease and thus increase the underlying anxiety and lead to an increased neurosis and invalidism. Bradycardia as a result of emotional stimulation occurring during dreams has been recorded. Although psychological factors may be related to some cases of paroxysmal atrial fibrillation and flutter existing data do not warrant conclusions on this point at the present time.

**Murmurs**—There is no evidence to suggest that psychological factors are of any etiological significance in the development of cardiac murmurs of either the organic or functional type. However they may be of profound importance in the establishment or increase of disability by neurotic mechanisms. It is an unfortunate fact that in the mind of the laity a diagnosis of murmur has become nearly synonymous with cardiac invalidism, because of this it has become doubly important for the physician to assess and treat each case in terms of isolated phenomenology such as the presence of a murmur. Insistence of full activity within the limits of the patient's capabilities and strong reassurance will do much to counteract the tendency of the patient to drift into a state of invalidism.

Other symptoms such as giddiness, headaches, syncope, fatigue, weakness and insomnia may accompany organic disorders of the cardiovascular system. When present they may be the result of morbid physiology arising from the organic lesion or they may be psychogenic in origin or they may be the manifestations of a combination of the two causes. The role played by each factor usually may be determined by a careful history but at times intensive investigation is necessary to establish the source.

While a thorough discussion of the psychodynamic constellations and psychophysiological factors involved in diseases of the cardiovascular system is beyond the scope of this book, some of the salient features may be mentioned.

### Emotional Effects on the Normal Heart

**Cardiac Neurosis**—Aside from the transient effects of normal emotions upon the normal heart there is a large group of people who have a number of symptoms related to the heart which cannot be attributed to organic lesions. The symptom complex is generally referred to in the current literature as cardiac neurosis. Although this condition would be described more accurately as neurosis with cardiac manifestations the current nomenclature has become so firmly entrenched as to make a change improbable.

In this group of patients the symptoms complained of are most commonly pain, dyspnea, palpitation, precordial discomfort, fatigue or some of the other manifestations discussed above. Often there are frankly expressed fears of heart disease, sudden death, invalidism or work incapacity and usually the patient evidences manifest anxiety although at times the anxiety is completely masked. Characteristically the complaints are out of proportion to the objectively observed disability whereas the patient with an organic heart disorder tends to minimize the degree of disability which he experiences. In neurotic disorders it is unusual to find any objective evidence of a dis-

ordered function of the heart other than a minor degree of tachycardia of a variable character, occasionally extrasystoles at times subjective complaints of precordial tenderness, or pulse lability with emotion. Proper differential diagnosis must rest upon the history of a neurotic background, the relationship of neurotic cardiac manifestations to this background and to the current stresses and the absence of objective findings of an organic nature. The diagnosis of cardiac neurosis must not be made solely on the basis of exclusion of organic disease.

In general, psychogenic cardiac manifestations are found in conjunction with anxiety or with an anxiety neurosis and the major psychological conflicts involved in this process have been discussed above. However in some individuals the only manifest evidence of anxiety will be that of the cardiac symptoms. It is in such cases that one finds that the conflicts are of a totally unconscious nature and that the individual has successfully repressed every evidence of the conflict other than psychosomatic phenomena. In this latter and numerically less frequent group, intensive psychiatric investigation may be necessary before the psychogenic origin of the symptoms can be made evident. Whereas the majority of the cardiac neuroses are related to anxiety neurosis it is not uncommon to find phobic and, less commonly, hypochondriacal, obsessional or delusional processes at the root of the cardiac complaints. The discussion of these psychodynamic mechanisms belongs more appropriately in the realm of psychiatry and psychoanalysis.

**Neurocirculatory Asthenia**—This disorder which has been variously called neurocirculatory asthenia (see page 373), soldier's heart, disordered action of the heart (DAH), nervous heart, etc. was described by Da Costa during the Civil War and is largely a disease of military life although it is believed to occur in civil life as well. Although this condition is usually described as an individual entity, most of the present day evidence points to the fact that it is in reality a form of the cardiac neuroses described above. Neurocirculatory asthenia (NCA) is usually depicted as occurring in a thin, inadequately muscled asthenic individual who has a lifelong history of avoidance of strenuous and competitive exercise and who is often labeled as 'constitutionally inferior'. It must be kept in mind that the reason for avoidance of strenuous exercise and competitive activity and thus an inadequate development of somatic and cardiac musculature may be entirely neurotic in origin rather than constitutional. In many of these individuals it is not uncommon to find a history of neurotic dietary limitations in these patients and this would of course tend to limit further their physical development and reserves.

On a situational basis NCA patients may be divided into two major groups: (a) those who develop symptoms under a minimal physical and emotional stress and (b) those who develop symptoms only under severe emotional and/or physical stresses. The former tend to recover from their symptoms less rapidly when they are removed from the stressful environment and given adequate psychotherapy because as one might expect their more limited tolerance of stress is usually found to be accompanied by a more profoundly neurotic background. In the second group recovery usually occurs



rapidly upon removal from the exhausting environment and with the institution of adequate food rest and psychotherapy.

The main symptomatic characteristic of this group of patients which appears to differentiate them from the cardiac neurosis group is the response to exercise. Details of this abnormal response to exertion will be found elsewhere in this text-book. In general the differences between the exercise responses of the NCA group and the cardiac neurosis group are quantitative but not qualitative. Varying degrees of exercise intolerance are frequently noted in patients proved to have a cardiac neurosis. Adequate explanation of the mechanisms involved in the abnormal exercise tolerance does not exist at the present time but it appears probable that endocrinal and autonomic dysfunction may play an important role and it is well established that emotional conflicts may profoundly influence both of these systems.

In a study of Wittowers it was demonstrated that none of the NCA patients examined could be considered to be well adjusted emotionally. A major portion of these patients who exhibited gross neurotic manifestations prior to the onset of the effort syndrome indicated that phobic mechanisms were of prime importance in their disorder. In many instances this appeared to be related to claustrophobic reactions and thus in turn with the feelings of suffocation complained of by the patient. Whether the peptic ulcer patient is often concerned with problems of economic security and the colitis patient with matters of cleanliness and orderliness these individuals must deal with conflicts which revolve around aggression and the need to maintain rigid standards of ethics morality and performance. More specific details about this heterogeneous disorder will be found in the references given.

Psychotherapy is the most important single consideration in the treatment of the cardiac neurosis and neurocirculatory asthenia. In many instances excellent results can be obtained without the use of formal verbal psychotherapeutic techniques; in other cases orthodox verbal psychiatric methods will be required. Decision on this point can be made only after careful assessment of the depth and severity of the neurotic factors in each case. In all patients it is absolutely essential to assure the individual about the absence of an organic heart disorder as soon as reasonable examination has indicated this. In general the cardiac neurotic tends to overprotect himself and to restrict his activities unduly because of his fears about his heart. It is usually necessary for the physician to insist upon a reasonable amount of exercise and activity for such patients in order to limit the tendency toward invalidism. Reassurance as to the lack of danger in connection with symptoms experienced during activity will do much to assist in keeping the individual active. Unusual amounts of rest are warned against in these neurotic patients. Supportive measures of a general nature are discussed elsewhere in the book. Mild sedation may be useful when anxiety is prominent but the tendency to use it routinely must be deprecated.

### **Emotional Conflicts and the Diseased Heart**

**Angina Pectoris**—It is generally conceded that the symptoms of angina pectoris are due to an insufficient oxygen supply to the heart muscle and that this insufficiency is due to a narrowing of the coronary arteries. This

narrowing may be of a transient nature and be the result of muscular contraction under the influence of the autonomic nervous system, or it may be the result of tissue pathology in the walls of the coronary arteries and thus be of a permanent character. There is clinical and experimental evidence which indicates that emotional stimuli acting through the autonomic nervous system may markedly alter the rate and volume of blood flow through the coronaries and produce anginal symptoms. The hypothesis of those who consider that emotional conflicts may play an important etiological role in the development of angina pectoris is as follows. Unconscious conflicts acting through the vegetative nervous system may produce coronary spasm and the disastrous symptoms and effects of angina pectoris in some individuals. Recurrent spasm may lead to petechial hemorrhages in the wall of the coronaries and thus eventually to permanent tissue pathology and death in others. While there is evidence of a subsidiary nature to support this thesis the evidence is by no means complete nor does it indicate that this is the sole method concerned in the development of angina pectoris.

Aside from the possible etiological significance of psychogenic factors there is much evidence to indicate that when anginal symptoms have made their appearance from any source marked degrees of anxiety usually appear. The anxiety may be a simple result of the very real fears of pain and death but it may also be reinforced by the unconscious emotional conflicts of the individual. Whatever the source of the anxiety it tends to increase the frequency and severity of the attacks and undoubtedly contributes to the progression of the disease by means of the psychophysiological coronary reflexes indicated above.

Psychiatric surveys of patients with anginal symptoms have indicated that the personality structure of these individuals is similar in many respects to that of those persons who suffer from coronary thrombosis. The average patient with either condition tends to have powerful conflicts over authority, but whereas the anginal patients tends to try to be as good as his superior and to imitate the father rather than trying to outdo him the coronary patient tries to subdue and to be the boss of others. In the pursuance of authority both of these patients are driven to work almost compulsively and have little time for other activities. Their intense need to dominate and to control completely their own activities often leads them to disregard the advice of the physician and they usually attempt to disguise or reject any disabilities because it tends to interfere with their drive for dominance. In both disorders it is common to find a history of emotional shock preceding the onset of the disease. This shock often takes the form of a sudden death in a near friend or relative or it may result from reverses in the striving for authority. The picture presented above is a composite one and individual cases may show marked divergence from the pattern.

While psychotherapy is highly desirable it must be undertaken with the utmost of caution for overenthusiastic investigation may intensify underlying conflicts and lead to an increase in symptoms or even death. In more advanced cases it is often wise to depend on superficial supportive psychiatric measures, such as reassurance and advice about current problems rather than

to attempt formal verbal psychiatric investigation and therapy. When formal psychotherapy is deemed advisable it should be undertaken by a skilled psychotherapist working in conjunction with an experienced internist. One of the major therapeutic goals in these patients is the diminution of unreasonable fears and the reestablishment of hope.

**Coronary Thrombosis**—The frequency with which traumatic emotional stress precedes the onset of coronary thrombosis by a short time and the high degree of similarity in the character traits of these patients strongly suggests that emotional factors may play an important role in the etiology of coronary thrombosis at least in some cases. When emotional conflicts are active in this process it is probable that they act through the autonomic nervous system to alter the coronary blood flow, the blood pressure and perhaps the rhythm and rate of the heartbeat. Although these psychophysiological reactions have been directly observed in a few cases, adequate psychodynamic and psychophysiological formulations are only in a hypothetical phase of development at the present time. Further studies will undoubtedly clarify this problem in the future.

As indicated in the discussion of angina pectoris, there is a strong similarity of personality structure in the patients of these two groups. The major difference between the two appears to be mainly a quantitative variation in the realm of hostility, whereas the anginal patient tended to equal his rivals, the coronary patient seemed to be more strongly driven to subdue and surpass. In her study of coronary patients, Dunbar reports that no patient was found to have a good relationship with the father and it is probable that this rivalry represents the prototype of the continuing struggle to equal or surpass any authoritative figure, particularly in the field of business. In the group of coronary cases there was a more than threefold exposure to sudden death due to cardiovascular and other accidents in the males of the family and we know that such an occurrence in conjunction with powerful unconscious hostile wishes towards that person usually leads to profoundly disturbing emotional conflicts. These problems of hostility are usually found to be much more completely repressed in the anginal and coronary patient than is the counterpart which occurs in the patient with hypertension. While these statistical findings are useful for theoretical purposes, their application to the individual patient is limited because of the wide psychodynamic variation among individuals.

The psychological sequelae and psychotherapeutic considerations involved in coronary thrombosis are the same as those discussed under angina pectoris.

### **Emotional Factors in Hypertension**

In the following discussion we shall be concerned with emotional factors involved in essential hypertension; consideration of hypertension due to known organic factors such as anatomical defects, primary renal disease, tumors, endocrine dysfunction, intoxications, etc., will be omitted. It is conceded by most observers that the chronic elevation of blood pressure in essential hypertension is the result of an increase in tone of the arterioles of the body, particularly in the splanchnic area. Further, it seems probable that the later anatomical findings such as the thickening of the arteriolar

walls increased heart size and others are a result rather than a cause of hypertension. There are two major hypotheses as to the origin of this increase in arterial tonus. The neurogenic theory holds that it is a result of an increased or disordered activity of the visomotor centers while the humoral theory considers that the increased tonus is brought about by the elaboration of a pressor substance somewhere in the body possibly in the ischemic kidney. Those who believe that the psychogenic factors are at the root of the disorder are of the opinion that the humoral and neurogenic mechanisms, which are not mutually exclusive are the intermediary means through which emotional conflicts can produce hypertension.

There is an increasing body of evidence to support the belief that emotional conflicts may be of primary importance in the development of hypertension. Cannon and many other observers have demonstrated that rage and fear in animals and humans are followed by an elevation of blood pressure of a transient nature. Longitudinal studies of essential hypertension have shown repeatedly that in the early stages the blood pressure rises and remains elevated for a transient but variable length of time, gradually the basic level of the blood pressure increases and the transient rises no longer return to the original level. It seems probable that in the early and reversible stage the increase in pressure is due to an increased tonus of the arterioles, and as the disease progresses tissue alterations in the walls of the arterioles begin to make the elevation in blood pressure irreversible. Psychiatric studies of a number of patients in the early stages of hypertension have demonstrated that there is a direct correlation between the periods of emotional tension and elevated pressure and conversely between periods of emotional calm and normal blood pressure. In the psychoanalytic treatment of a few cases of early hypertension two patients have been reported as having had their blood pressure return to normal levels apparently permanently and others have evidenced a lowering of blood pressure. Since spontaneous remissions of hypertension are not rare it is far too early to evaluate the meaning of this and much more evidence is needed before the psychogenic causation of essential hypertension can be accepted as proved (see page 446).

In studying the psychological aspects of essential hypertension Alexander and his coworkers Saul Weiss and others have demonstrated that there are certain psychodynamic constellations which appear in most patients with this disorder who have been studied. Although the number of patients so far investigated by psychoanalytic methods is still too small to warrant conclusions of a general nature the following salient features are reported by Saul

(a) In every case there was a dominant mother with a need by the patient for submissiveness and oral dependence toward her. In the male patient this is transferred to the father and there is a resultant hostility and ineffectual rebellion against the need for submission. Rage because of the unsatisfied oral demands and because of the need for independent activity can not be expressed.

(b) The hostility developed becomes chronic inhibited and powerful but is not adequately repressed. It is near to the surface yet cannot be acted upon nor evaded.

(c) Heterosexual activity is inhibited and when indulged in usually gives rise to unrecognized anxiety.

(d) Although the conflict between passive dependent wishes and active, destructive hostile wishes occurs in other psychopathological entities it is the inability of the patient to satisfy either demand consistently which characterizes the hypertensive. He is blocked in both directions and can express neither. Satisfaction of either the passive dependent impulses or of the hostile urges leads to a lowering of the blood pressure during the period of such satisfaction.

The elucidation of the specific psychodynamic mechanisms related to hypertension will require further investigation and indeed there is as yet no conclusive proof that any specific psychodynamic mechanism can be directly correlated with any single physiological reaction in all instances.

While the effectiveness of psychotherapy as a means of permanently altering the blood pressure is undetermined at the present time there can be little doubt that some form of psychotherapy is not only desirable but essential in the proper management of essential hypertension. In our current civilization almost all people are emotionally disturbed by the mere diagnosis of 'high blood pressure' and many of the symptoms which appear during the course of the disease may be the result of the emotional disturbance rather than the hypertension. Furthermore it is probable that these conflicts may even affect the hypertensive process adversely. Much can be accomplished by reassurance of the patient by inducing him to solve his current conflicts particularly when they involve hostility by allowing him to give free vent to his hostile thoughts and by allowing him to form a certain amount of dependence upon the therapist. Some understanding of the patient's problems and a rather sympathetic permissive attitude on the part of the physician will do much to accomplish these aims in many instances. Medical and surgical indications and therapies are considered elsewhere in the book.

**Hypotension**—It is believed by many that a number of cases of so called hypotension have a large psychological factor present in their illness. This may be of importance etiologically or it may contribute materially to the amount of disability accompanying the disorder. Adequate psychiatric studies have not been done up to the present time.

## GASTROINTESTINAL SYSTEM

### Upper Gastrointestinal Tract

Statistical surveys of disorders of the upper gastrointestinal tract made by various observers have indicated that from 25 to 40 per cent of such complaints are functional in origin. Even though these studies do not take into account the fact that certain so called organic diseases such as peptic ulcer may eventually be proved to be psychogenically initiated the importance of psychological factors is evident. That emotional stimuli are involved in the function and dysfunction of the gastrointestinal system should not be an occasion for surprise when consideration is given to two facts: (a) the richness of the autonomic nerve supply to the gastrointestinal tract and (b) the

walls increased heart size and others are a result rather than a cause of hypertension. There are two major hypotheses as to the origin of this increase in arterial tonus. The neurogenic theory holds that it is a result of an increased or disordered activity of the vasomotor centers, while the humoral theory considers that the increased tonus is brought about by the elaboration of a pressor substance somewhere in the body, possibly in the ischemic kidney. Those who believe that the psychogenic factors are at the root of the disorder are of the opinion that the humoral and neurogenic mechanisms which are not mutually exclusive are the intermediary means through which emotional conflicts can produce hypertension.

There is an increasing body of evidence to support the belief that emotional conflicts may be of primary importance in the development of hypertension. Cannon and many other observers have demonstrated that rage and fear in animals and humans are followed by an elevation of blood pressure of a transient nature. Longitudinal studies of essential hypertension have shown repeatedly that in the early stages the blood pressure rises and remains elevated for a transient but variable length of time. Gradually the basic level of the blood pressure increases and the transient rises no longer return to the original level. It seems probable that in the early and reversible stage the increase in pressure is due to an increased tonus of the arterioles and as the disease progresses tissue alterations in the walls of the arterioles begin to make the elevation in blood pressure irreversible. Psychiatric studies of a number of patients in the early stages of hypertension have demonstrated that there is a direct correlation between the periods of emotional tension and elevated pressure and conversely between periods of emotional calm and normal blood pressure. In the psychomimetic treatment of a few cases of early hypertension two patients have been reported as having had their blood pressure return to normal levels apparently permanently, and others have evidenced a lowering of blood pressure. Since spontaneous remissions of hypertension are not rare it is far too early to evaluate the meaning of this and much more evidence is needed before the psychogenic causation of essential hypertension can be accepted as proved (see page 446).

In studying the psychological aspects of essential hypertension Alexander and his coworkers Saul Weiss and others have demonstrated that there are certain psychodynamic constellations which appear in most patients with this disorder who have been studied. Although the number of patients so far investigated by psychomimetic methods is still too small to warrant conclusions of a general nature the following salient features are reported by Saul.

(1) In every case there was a dominant mother with a need by the patient for submissiveness and oral dependence toward her. In the male patient this is transferred to the father and there is a resultant hostility and ineffectual rebellion against the need for submission. Rage because of the unsatisfied oral demands and because of the need for independent activity cannot be expressed.

(b) The hostility developed becomes chronic inhibited, and powerful, but is not adequately repressed. It is near to the surface yet cannot be acted upon nor evaded.

**Belching**—In the absence of certain organic diseases, excessive belching is almost invariably the result of neurotic swallowing of air. It is generally used by the patient to reinforce his belief and the belief of others that his symptoms are due to local abdominal pathology rather than to the subjectively less acceptable neurotic conflicts. The symbolic meanings of aerophagia vary with the case.

**Indigestion**—The term indigestion is usually used to describe the subjective feelings which accompany lesser dysfunctions of the stomach whether they be of organic or psychogenic origin. Psychologically it rarely if ever has any specific meaning except in so far as it is related to nausea and vomiting.

**Anorexia**—Distinction must be made between appetite and hunger although they are usually closely associated and simultaneously stimulated. Either may stimulate the other. Hunger may be thought of as the somatic expression of physiological needs and appetite as its psychic counterpart. In organic disease the suppression of hunger manifestations usually accounts for the anorexia or loss of appetite. When anorexia occurs without the disappearance of hunger manifestations although the latter may be suppressed subsequently the origin of the disturbance is usually psychogenic. When anorexia appears it is usually due to inability on the part of the individual to accept a conflictual situation and is the symbolic representation of this difficulty. In psychotics it may occur as the result of suicidal drives and it may express similar wishes in certain neuroses. With rare exception perversions of appetite are of neurotic or psychotic origin.

A number of studies have indicated that psychological factors may be of importance in disorders of the upper gastrointestinal tract. At the present time some discussion of these factors is warranted for the following conditions: gastric neurosis, gastritis, peptic ulcer, cardiospasm, chronic cholecystitis and anorexia nervosa. The organic factors related to these conditions and their symptomatology are discussed elsewhere in the book.

**Gastric Neurosis**—The term gastric neurosis is in reality a misnomer for the symptoms manifested are but a part of the process of a much more widespread and deep seated neurotic process which affects not only the stomach but the whole behavior and function of the individual as well. For psychological reasons the major complaints may be related to the gastrointestinal functions but any investigation of a more than cursory nature will always reveal that the disorder contains psychopathological phenomena and often other psychophysiological dysfunctions as well. Since the term is a broad one it may be used to delineate a spectrum of conditions ranging from symptoms of a fantasied nature without discernible gastric physiological dysfunction to those conditions of psychogenic origin with measurable physiological alterations. In this latter group are the conditions such as the so called dyspepsia and some of the gastritides of nonorganic origin in which investigation will reveal an actual gastric hyperemia, hyperacidity or hypermotility of a variable degree of intensity and duration. Local hypofunction may also be found. Thus we see that in this condition of gastric neurosis symptoms may be due to pure psychological formulations or to a combination

powerful associations formed in the mind of the infant between being fed on the one hand and being loved and protected on the other. Everyday life bears constant witness to psychophysiological reflexes such as salivation and gastric activity when thinking of food in a hungry state, and not infrequently one is aware of the hyperacidity accompanying anxiety, the nausea of disgust the slowing of digestion with sorrow and so on. All of these experiences give evidence of the constantly recurring effects of transient emotion upon the functions of the gastrointestinal tract. In extension of this knowledge there are many who believe that chronic emotional disturbance can lead to chronic disturbance of function of the gastrointestinal tract and through this to local tissue alteration.

Most psychiatric studies of the emotional factors related to dysfunction of the gastrointestinal tract have indicated that consciously experienced emotions such as anger, fear, sorrow, and others have only a transient somatic effect and it is generally true that emotional conflicts of a conscious nature can be dissipated by appropriate voluntary activity and so cease to be effective as stimuli producing somatic repercussions. It is the opinion of Alexander and a number of others that the major emotional factors concerned in the upper gastrointestinal disorders are of an unconscious origin, and of these conflicts those related to oral receptive and dependency needs appear to be of primary concern in the majority of cases. These psychodynamic mechanisms will be discussed in greater detail later.

Before the various disease entities are discussed some of the psychological factors related to the major symptoms of upper gastrointestinal disturbance will be presented. Among the symptoms of prominence are pain, nausea, vomiting, belching, anorexia and indigestion.

**Pain**—When pain and discomfort are experienced as the result of gastric hypermotility or hyperacidity of psychogenic origin they differ in no way from the pain and discomfort due to hypermotility or hyperacidity of organic origin for the pain producing mechanisms are identical in both cases. When the psychological stimuli are insufficient in intensity or duration to produce a significant local physiological dysfunction the patient usually complains of pain or discomfort which is poorly localized and vague in type. This is commonly seen in so called gastric neurosis and it usually accords with the patient's ideas of what gastric pain should be. On close questioning the pain complained of is often found to be in reality a feeling of tension in the upper abdomen. Except when of delusional origin the pain complained of rarely has any specific psychological connotation.

**Nausea and Vomiting**—These symptoms can be considered together in that they are inextricably related in respect to their psychological significance. Almost without exception they represent in a symbolic way an attempt to reject or resist an unpalatable situation which cannot be faced consciously. This is beautifully demonstrated in many cases of hyperemesis gravidarum in which the woman attempts symbolically to rid herself of an unconsciously unacceptable pregnancy and fetus. (Lobus hystericus is usually found to arise from the same psychodynamic mechanisms as vomiting.)



they are of a deeply repressed oral character. Because of the infantile association between these needs and that of hunger and being fed the frustration of these unresistible demands for affection and security leads to a chronic reactivation of the psychophysiological responses normally associated with hunger i.e. the gastric hyperemia, hypersecretion and hypermotility. It is seldom that these oral dependent wishes can be consciously accepted because of the injury to self-esteem entailed and because of the guilt evoked by the primitive demanding regressive wishes, consequently the individual has usually cloaked these dependency wishes by repression and denial of them. By overcompensation in the form of exaggerated independence he often tends to seek economic security as proof of this self-sufficiency but when this conscious tangible security is threatened regression to more primitive dependency needs occurs and the unconscious conflicts are intensified. Thus we usually see the ulcer patient as a hard working apparently independent person who will consciously deny and reject any indication of his basic unconscious need of security. Other psychodynamic mechanisms are probably of importance but they have not yet been worked out.

Therapy may be directed towards the local lesion and may be medical or surgical in character. Recently, surgical measures have been directed at the intermediary mechanism the vagus nerve with some success and this procedure tends to confirm the importance of the autonomic nervous system in the genesis of peptic ulcer. Following the removal of symptoms by such a procedure depression and severe psychoneurotic symptoms have been known to appear and it must be kept in mind that symptoms often serve the purpose of acting as a safety valve against the development of more seriously disturbing disorders. In a curative sense deep psychotherapy appears to offer promise but at the present time a sufficient amount of data has not accumulated to warrant conclusions. More superficial psychotherapy can be of immense benefit in many cases and it involves assisting the patient in solving disturbing reality situations utilizing transference phenomena to permit the patient to develop a reasonable degree of dependency upon the therapist thus fulfilling in a limited fashion the patient's unconscious needs, and stimulating the development of activities which with the attainment of an increased proficiency bring in increased sense of security. Except in the hands of a skilled psychotherapist it is probably wise to avoid therapeutic investigations which lead directly into repressed unconscious material for if not controlled the emotional reactions liberated may lead to a serious exacerbation of symptoms or to the appearance of disturbing neurotic reactions.

**Cardiospasm**—Although there is much disagreement as to the etiology of this condition current evidence makes it probable that psychological factors are of significance in some cases. Here as in other gastrointestinal conditions it would seem that emotional conflicts may act through the vegetative nervous system to produce spasm of the cardiac sphincter at first transient and then chronic or recurrent. With chronicity the hypertrophy of the sphincter and the atony and enlargement of the esophagus develop as sequelae. The initial episode can often be traced to the occurrence of some traumatic emotional situation which the individual cannot free, and with recurrence of situations

of these plus actual physiological dysfunctions. The mechanisms by which the latter are produced will be discussed briefly under peptic ulcer.

The symptoms of gastric neurosis, which are discussed elsewhere in the book (see page 626) may stem from conflictual mechanisms involving threats to security and dependency wishes and are often accompanied by the affects of anxiety, fear, anger, disgust, or sorrow although the conscious awareness of these feelings may be minimal in some cases. Gastrointestinal complaints may appear as a part of anxiety reactions, hysteria, hypochondriasis or less frequently as delusional manifestations in a psychosis, and again they may or may not be accompanied by actual physiological alterations. If the current psychoanalytic formulations are correct, the central psychological theme in this disorder is the existence of threats against the strong oral needs for affection, dependency and security. Although these psychodynamic mechanisms have been found to be operative in a number of cases the evidence is insufficient to allow a general application of this thesis at the present time.

**Peptic Ulcer**—During the past few decades an increasing amount of direct and subsidiary evidence has made it apparent that emotional factors may be of primary importance in the genesis of peptic ulcer in many patients. A number of studies have indicated that there is a direct relationship between various emotions and the motor, vascular and secretory activity of the stomach in man and in animals. The classic studies of Wolff and Wolf in a patient whose persistent gastrostomy permitted continuous visualization of the gastric mucosa clearly demonstrated that specific mucosal, secretory, and motor changes regularly accompanied certain emotional states. For example in situations which engendered anxiety there was a marked degree of hyperemia, hyperacidity and hypermotility which persisted as long as the threat of loss of job which led to the anxiety. Even more importantly it was noted that during such states of mucosal hyperactivity the tendency towards petechial hemorrhage and ulceration was greatly increased and the ulceration tended to persist. Thus it was established that an abnormal status of the gastric mucosa of psychogenic origin predisposed to the formation and persistence of ulceration.

The hypothesis of the exponents of psychogenic causation in peptic ulcer may be summarized briefly as follows. Certain emotional conflicts in some individuals may stimulate the autonomic nerves of the stomach in a specific fashion and thus produce alterations in the gastric motility, secretions and vascularity which predispose to ulceration. The ulceration may be brought about by chemical, thermal or mechanical irritants but it is the abnormal state of the mucosa which makes the ulcer slow to heal and this abnormal mucosal condition will persist as long as the irritating emotional conflicts remain active. Alexander, his co-workers and others believe that there may be specific psychodynamic constellations related to the gastric dysfunction which predisposes to peptic ulcer and the psychoanalytic material uncovered thus far tends to bear out their assumptions. In summary the conflicts common to the patients they have studied are as follows. There are powerful unconscious wishes to be fed, loved and cared for usually by the mother. These demands may be of a passive receptive or aggressive demanding nature and

strated that alterations in colonic function such as changes in tonus and peristalsis, mucosal engorgement and blanching, increased or decreased secretion of mucus and lysozyme and mucosal patchy hemorrhages may all appear as a result of emotional stimulation. As in disorders of the upper gastrointestinal tract, it is assumed by an increasing number of physicians that while transient colonic dysfunction is produced by acute emotional disturbances, chronic emotional conflicts may lead to chronic dysfunction and through this may produce local tissue alteration in the colon of certain individuals. In the succeeding discussions disorders of the colon due to known organic diseases such as enterocolitis, typhoid fever, poisons, parasites etc. will be excluded.

In disorders of the colon four symptoms are of major importance: pain, hemorrhage, diarrhea and constipation. Psychological factors usually are of importance only in the latter two.

**Diarrhea**—As mentioned above, transient frequency of bowel movement or diarrhea may be produced by emotional stress. If such manifestations are transient they are not of importance, although when the psychological stimulus is minor it is usually found that those individuals who develop diarrhea have an unstable emotional background. When diarrhea of this type occurs it is probable that an increased colonic peristalsis as a result of autonomic stimuli of psychogenic origin is responsible. In the absence of a responsible organic condition, chronic diarrhea of psychogenic origin is known to occur and it is usual to find that the related emotional conflicts are deeply buried in the unconscious and are of a primitive nature. In a psychoanalytic sense these conflicts are concerned in some cases with a need for giving in a symbolic way as a restitution for symbolic oral taking of a hostile nature. Psychological regression to the anal phase of development is involved.

**Constipation**—In the absence of organic causation this extremely common condition is perhaps best regarded as a symptom rather than as a specific disease entity. While there may be a certain value from the standpoint of chemotherapy in dividing constipation into spastic, atonic and dyschezic types, it is doubtful that such categorization has any etiological significance. It is often stated that neurogenic and habit mechanisms are responsible for the colonic variations and it is probable that this is true. However, this explanation does not seem to go far enough in the majority of cases for it leaves the origin of the autonomic dysfunction and of the habits unexplained. It is probable that in many instances neurotic conflicts can be found at the root of the autonomic imbalance and the improper bowel habits. Psychoanalytic studies of some cases have demonstrated that in part it may be due to a desire to withhold a symbolically valuable part of the body and that the process of retention may be related to a primitive sexual urge of an anal character. It is known that primitive anal regressive mechanisms play an integral role in most paranoid psychoses and it is interesting to note that 72 per cent of such partial confirmation of psychosomatic ideas about constipation cases had constipation whereas constipation was found in only 26 per cent of a control group.

which impinge upon the basic conflicts there is a recurrence of the spasm. While sufficient data are not yet forthcoming, it appears probable that the basic psychodynamic problems are based upon conflicts of an oral nature, and that they are situations which in a symbolic sense the patient cannot 'swallow'. It is probable that psychotherapy would be of real benefit in the treatment of this condition, particularly in the early stages. This may be carried out in conjunction with such measures as mechanical dilatation in the later stages of the disease.

**Anorexia Nervosa**—All of the physical symptoms and signs exhibited in this interesting disease can be explained on the basis of the undernutrition which characterizes it. In the absence of primary organic disease such as destruction of the pituitary gland, it is probable that the lack of appetite and the avoidance of food which lead to the inanition are due to psychological factors. Severe psychoneurotic and even psychotic processes are invariably present in such individuals. The emotional conflicts involved in this disorder are varied. Not infrequently there are unconscious fears of oral impregnation, marked inhibition of heterosexuality or ideas in which obesity and pregnancy are equated, because of fears of sexuality and pregnancy and the unconscious relationship of such activities with normal or obese body configuration. The patient starves herself to prevent the possibility of such happenings occurring to her. At times powerful unconscious hostility leads to marked guilt reactions and suicidal impulses in the unconscious lead to starvation as a means of attaining this goal. In certain schizophrenics the attempt to withdraw from reality leads to the avoidance of food along with other manifestations of reality. In conditions with severe oral conflicts not unlike schizophrenia there may be a failure in ego development and anorexia nervosa may occur during periods of emotional stress particularly when dependency relations to the parent are threatened. In all of these conditions it is probable that the starvation creates some endocrine dysfunction and this in turn increases the loss of appetite. Psychotherapy in conjunction with attempts to maintain nutrition is the only measure which offers prospect of success in this condition and because of the severity of the psychiatric disturbance psychotherapy is often difficult.

**Chronic Cholecystitis**—Although there is evidence to the effect that psychic factors may markedly increase or decrease the rate of flow of secretions from the biliary tract the psychological factors related to cholecystitis have not been adequately studied. Wittkower has demonstrated that annoyance produced cessation of biliary flow in the patients he studied and clinicians have noted that there is a high incidence of emotional situations which produced annoyance just preceding the first two or three attacks of biliary colic in a large series of cases. This relatively unexplored field is in urgent need of exploration.

#### Lower Gastrointestinal Tract

It has been common knowledge for centuries that frequent bowel movements or diarrhea may be the result of certain emotional stimuli such as anxiety or fear. Less well known is the fact that constipation may also be of psychogenic origin. Experimental and clinical investigation has demon-

tion increased lyszyme production or other enzymatic reactions. While all of this has not been proved a number of clinical and experimental observations make it probable that this or a very similar chain of events occurs in the development of ulcerative colitis.

The studies of Murray Lindemann, Groen Ross and others on the personality structure of patients with ulcerative colitis indicate that with minor variations there is essential agreement on the basic psychological structure of most cases. All of the patients give evidence of profound psychoneurotic mechanisms with psychotic characteristics not far from the surface in a number of them. Hysterical depressive and compulsive reactions are predominant and manifestations of the anal phase of development such as rigidity, overtidiness and masked hostility are prevalent. While these patients are superficially pleasant and cooperative as a rule powerful hostility and marked overdependence upon some central figure are almost invariably found under this apparently unperturbed surface. In from 50 to 75 per cent of the cases the onset of exacerbation of the disorder follows closely upon the loss of the loved person either through estrangement, departure or death. This breach of dependency relationship is of the utmost importance in these individuals not only from the standpoint of dynamics but also from the fact that successful psychotherapy must be based upon it.

Numerous medical and surgical remedies have been used in the treatment of ulcerative colitis with indifferent success. It is becoming increasingly evident that psychotherapy must be an integral part of the management of these patients if success is to be attained. The essential point in psychotherapy is the establishment of a strong transference relationship to the therapist so that he may replace the lost love object upon whom the patient has been so profoundly dependent. This is best accomplished not by verbal exploratory psychotherapy but by a sympathetic noncritical support of the patient in which the therapist takes the role of a firm kindly parent and assists the patient with his problems. To this end all supportive measures such as sympathy reassurance massage warm baths simple feeding routines and symptomatic medication may be desirable. Gradually after the acute manifestations have subsided a slow reeducation of the patient towards dependency upon some more normally related person may be attempted. Psychotherapy of the verbal type must be kept to a minimum during the acute phases of the disease and it must be limited to material which the patient uncovers voluntarily even then the brakes must be kept on and at the slightest sign of increase in somatic symptoms it must be terminated. *The only reliable guide to therapy is the increase or decrease in somatic symptoms.* Even during the quiescent stages of ulcerative colitis verbal exploration of unconscious conflictual material must be undertaken with the utmost of caution. Injudicious exploration can only lead to an exacerbation of symptoms and even death or it may replace the somatic manifestations by an even more disabling psychosis. It is characteristic of these patients that the somatic disorder often exists as an alternative to a psychosis and this dilemma may also exist in some of the other more serious psychosomatic disorders such as arthritis hypertension peptic ulcer anorexia nervosa obesity asthma and others. The efficacy of

Of the various disorders of the lower gastrointestinal tract the psychological factors will be discussed briefly in Mucous Colitis and Ulcerative Colitis.

**Mucous Colitis**—The investigations of White, Cobb and Jones, Boekus, Bink and Wilkinson, Alexander and others have indicated almost beyond question that the manifestations of mucous colitis are the result of the effects of an overactive parasympathetic system upon the motor and secretory mechanisms of the colon. They further indicate that it is highly probable that the overstimulation of the parasympathetic nerve supply to the colon is psychogenic in origin. Their studies show that there is a high incidence of neurotic manifestations in those patients with this affliction and that for the most part the neuroticism antedates the disease; that emotional traumata often preceded recurrences or exacerbations and the patients were often aware of this connection. Phobic, compulsive and depressive symptoms were among the most common neurotic manifestations noted. Alexander and his coworkers, after careful psychoanalytic study of a small group of cases, came to the conclusion that they could be divided into two main psychological groups: the colitis group and the constipation group. The essential psychodynamic features of these two groups are given in part under the discussions of the symptoms "Diarrhea" and "Constipation." It is probable that many cases of mucous colitis have unconscious conflicts which are closely related to those described by Alexander. For elaboration of these concepts the reader is referred to the original articles.

Although symptomatic measures may be necessary in the treatment of this disorder, the major reliance should be placed on psychotherapy. In the more chronic and severe cases deep psychotherapy may be required, but in others more superficial psychotherapeutic procedures are often of considerable value. These should include explanation in simple terms of the emotional origin of the disorder, advice in the solution of the known conflicts and measures directed towards strengthening the defenses of the individual. A sympathetic, noncritical attitude which permits the patient to discuss freely his worries and fears may be of immense value.

**Ulcerative Colitis**—Ulcerative colitis is another disorder in which the profound organic changes tend to make the physician skeptical of the possibility of psychological factors being important in the etiology. While it is not here contended that emotional disturbances are the sole source of pathology, the psychiatric and psychological data which have accumulated strongly suggest that emotional factors are of real importance if not essential to the development and continuation of ulcerative colitis. The hypothetical means by which this is believed to come about is in summary as follows: Disturbing emotional traumata of a relatively specific sort act to intensify unconscious conflicts in these individuals. This emotional stimulus activates the autonomic nervous system to produce the bodily hyperemic, hypersecretory mucosa and the over-sensitive, hypermotile colon. Upon this morbid base petechial hemorrhages in the mucosa, either spontaneous in origin or from minute mechanical traumata, become ulcerated and the ulcers do not heal in certain individuals because of undetermined factors which may include specific or nonspecific infection.

following factors to be of significance. The patients had a remarkably close psychological dependence upon a parent, lover, or child and tended to bind them by a smothering affection and overdependence. A schism in this relationship was often related to the onset of the disorder and without repeated evidence of their importance to others the patients were inclined to feel helpless and hopeless. It is probable that these factors are not enough in themselves to produce the hyperthyroidism. Factors such as organic predisposition may be involved as well. Certainly further investigation of the psychophysiological relationships in hyperthyroidism is needed before dogmatic assertions as to etiology can be made. However, the findings are sufficient to warrant the need for a thorough investigation of the psychological status of each hyperthyroid patient. Evidence already exists to indicate that psychotherapy may be of real benefit to many patients with hyperthyroidism and in some of these individuals particularly the relatively nontoxic ones the toxicity has disappeared and the basal metabolic rate has returned to normal with no other treatment than psychotherapy.

The symptoms of hypothyroidism may be closely simulated by neurotic manifestations and this is particularly true of those patients whose basal metabolic rate is on the border line of normal. Psychoneurosis should always be thought of as a possible cause for symptoms in the lesser degrees of hypothyroidism whether or not there is a related depression of thyroid function in some of these patients has not been sufficiently studied.

**Islands of Langerhans.**—The regularity with which hyperglycemia accompanies certain emotional states such as fear and rage makes it apparent that psychological factors are closely related to the function of the glucose regulating mechanisms of the body. While this altered glycaemic state is known to be due in part to the secretion of adrenalin there is evidence to indicate that the insulin producing mechanisms are involved as well. In spite of the fact that this information has been available for some years relatively little attention has been paid to the possible relationship of psychological factors to diabetes mellitus. W. C. Menninger who undertook a psychiatric evaluation of a small group of diabetic patients was able to demonstrate that the course of the glycaemia and glycosuria paralleled the mental status and that with emotional recovery the diabetic condition cleared up insulin and dietary therapy no longer being required. Although the factors of long continued anxiety and fatigue passive personality tendencies and depression may be of importance in relation to diabetes, there is little information about psychological constellations which bear any specific relation to diabetes. It is probable that emotional conflicts lie at the root of the dietary indiscretions and the mismanagement of insulin which so disturb the regime of certain diabetic patients. Psychotherapy may be of material assistance in solving this problem.

Recently evidence has appeared which suggests that there is a direct relationship between hypoglycemic states and neurotic conflicts in some individuals. More investigation will be needed in the psychosomatic mechanics of diabetes and hypoglycemic states before a clear understanding can be obtained.

psychoanalysis in the treatment of ulcerative colitis has not yet been properly assessed although preliminary reports are encouraging. Even with psychoanalysis it is evident that it would be unwise to begin such therapy during the acute stages of the disease, and therapy must be governed by somatic symptoms at all times.

**Chronic Appendicitis**—While adequate psychological studies of this condition have not been made it is evident to the most casual observer that many in whom appendix has disappeared under the knife for symptoms which were entirely neurotic in order or derived from minor psychogenic disturbances of the colon.

## ENDOCRINE SYSTEM AND METABOLISM

The endocrine system and metabolism occupy an unusual role in the field of psychosomatic medicine for not only are the various glands subject to disorders of a specific nature but often they are also the intermediary mechanism between emotional disturbances on the one hand and dysfunction of special organs or organ systems on the other. Moreover, the functions of the various glands are so closely integrated and interrelated that a malfunction of one gland is often reflected in the disharmony of others and in an alteration in general metabolic efficiency. It is beyond the scope of this book to discuss the intricate interfunctioning of the neurohumoral systems and the emotions. Lancelotti has aptly described this as 'the disturbed chemistry of the unsatisfied person' and there is little doubt about the fact that emotional stimuli can and do affect endocrine function.

Every physician is familiar with the hypersecretion of adrenalin with fear and anger and the delayed menstruation of the woman in fear of pregnancy is common knowledge. In many articles on hyperthyroidism emotional trauma is mentioned as a precipitating factor and in certain patients the onset of diabetes has been attributed to emotional stress. It is probable that psychogenic stimulation of the gland through the autonomic system is the activating mechanism in some of these reactions and it is reasonable to assume that the various tropic hormones of the pituitary gland secreted under the influence of the emotionally stimulated hypothalamus may be the responsible factor in other instances. In the following discussions we shall concern ourselves only with the psychological factors believed to be related to specific endocrine glands and metabolic disorders. Dysfunction of primary organic origin will be omitted and only a few of the major diseases will be discussed.

**Thyroid Gland**—As previously mentioned emotional factors are referred to as a possible precipitant in hyperthyroidism but in the majority of these studies 'emotional factors' are used in a loose sense of the words and no adequate psychodynamic investigation has been undertaken. In those reports whose orientation was psychiatric the facts uncovered made it probable that psychological reactions were closely related to the appearance of the hyperthyroidism and may possibly be of etiologic significance in the disorder. Conrad in a study of 200 men and women with hyperthyroidism, found a history of apparently significant psychic trauma in 94 per cent of the cases. Lidz, whose findings are in agreement with Conrad's, believes the



up the gratification of eating frequently or large amounts. The complaint of irritability during the process of reducing is not uncommon and it is due probably to frustration of the emotional need to eat rather than to physiological reactions. One of the first aims in the treatment of obesity is to make the patient aware of the amount and frequency of eating. Awareness of the substitution of eating for other desired pleasurable activity is also a desirable goal. Psychotherapy is the only reliable means by which these ends can be attained.

### LOCOMOTOR SYSTEM

The reactions of the voluntary musculature to emotionally charged situations are a matter of almost daily observation. The play of expression upon the face in sorrow, joy, anger and apprehension and so on are so routinely seen as to all but escape conscious realization. Less obvious but equally common are the bodily postures accompanying various emotions and psychogenic alterations in muscular tonus are a matter of experimental record. From the standpoint of pathology it is probable that the muscular 'set' which accompanies fear and hostility is the most important. In the long development of evolution it has been essential for the survival of the individual that he be in a state of instant readiness to act either by flight, fleeing, or protective immobilization at the first warning of a threatening situation. This propensity for muscular preparedness has persisted to the present day and recent psychological investigations have shown that these reactions can be evoked by emotional threats as well as by physical dangers. It is the concept of many psychiatrists that when these phantasmal threats are chronic and unconscious they may be a persistent stimulus which produces a varying but continuous alteration in muscle tone. It is possible that this continuous increase in tonus may lead to pain and dysfunction and may be an integral part of the process which ends in arthritic changes. While there is strong evidence that psychogenic factors are of importance in that rather vague group of disorders which are combined under the lay term of 'rheumatism', convincing demonstration of the role of emotional conflicts in arthritis is not yet forthcoming. Nevertheless it has been demonstrated by Johnson and others that there are striking similarities in the personality structure of patients suffering from rheumatoid arthritis. The essence of these findings is that when the patient cannot discharge hostility by competing with or being of service to others the inhibited aggression finds outlet of an ineffective type in altered muscular tension and in arthritic reactions. The hostile state is believed to be a reaction to an early masochistic dependence upon the mother which is carried over into all human relationships. It is possible that the adrenal cortex may be involved as an intermediary agent in arthritis. (See discussion of the adrenal cortex.) None of these hypotheses contends that psychogenic factors are the sole origin of arthritis but psychotherapy has alleviated the symptoms and decreased the disability in a few cases. In short there is reason to believe that emotional factors may be of importance in rheumatoid arthritis and in related conditions.

**Adrenal Cortex**—It is well established that the adrenal cortex or its secretions are intimately related to the metabolism of glucose and nitrogen among other things. Selye and others have shown that the cortex is implicated in an important way in the response of the organism to stress whether it be of a physical or emotional nature. This he terms the "Adaptation Syndrome" and there is in the experimental evidence some suggestion that pathological conditions which are not dissimilar to disorders such as pericarditis, nodosa rheumatoid arthritis, certain lymphadenopathies and other disorders may represent the end result of a pathological adaptation to physical or psychological stresses. Whether or not this hypothesis is eventually proved to be true, there is little doubt that the response of the adrenal cortex to stress may be of profound importance in a number of psychosomatic conditions.

Little is known about the relationship of emotional factors to diseases of the adrenal cortex but it is well known that symptoms of lassitude, fatigue and weakness are often attributed to cortical dysfunction when they are in reality manifestations of a psychoneurosis.

**Other Glands**—While impotence and other disorders of a sexual nature are often attributed to hypofunction of the gonads, it is seldom that this is found to be true. By far the greater part of such problems lie entirely within the realm of psychiatry and for proper therapy it is mandatory that every patient with such complaints be given a thorough psychiatric evaluation. Dysmenorrhea has been found to be closely related to emotional conflicts usually basically sexual in nature in many individuals and there is strong evidence that psychological considerations may be of real importance in other gynecological conditions such as leucorrhea. In all of these genital and sexual disorders the emotional factors may be of importance not only from the viewpoint of etiology but also from the standpoint of complications and sequelae.

**Obesity**—One of the commonest ills of present-day civilization is that of obesity. It is usual for the individual so afflicted to protest that it must be glands. I scarcely eat a thing. In truth obesity is rarely glandular although after the characteristic endocrine alterations may be concerned in the site of deposition of the fat. Obesity is determined by one mathematical and inexorable rule: if the caloric intake exceeds the caloric output then weight is gained.

It has been found that the usual reason for excessive eating is almost invariably psychological. Eating is not only a reactivation of the primitive oral pleasure but also food may often be the symbolic equivalent of affection. Thus many individuals who find other sources of pleasure such as sex or affection denied them unconsciously turn to the more infantile gratification of eating as a pleasurable activity. In many obese women it has been demonstrated that the protuberant abdomen is a symbolic substitute for a desired pregnancy; in others femininity and pregnancy is feared and obesity serves the purpose of making them less attractive and thus in less danger of heterosexual sexuality.

The treatment of obesity is often troublesome because while the patient wishes to lose weight he is at the same time unconsciously unwilling to give

- Menninger K. Some Unconscious Psychological Factors Associated With the Common Cold *Psychoanalyst Rev* 21 201, 1934
- Osterlorf C I. Psychogenic Factors in Asthma *New York State J Med* 35 41 1935
- Saul I. Psychogenic Factors in the Etiology of the Common Cold *Internat J Psychoanalysis* 19 431, 1938
- Wilson, G W. Report of a Case of Acute Laryngitis Occurring as a Conversion Symptom During Analysis *Psychoanalyst Rev* 21 408 1934

#### Cardiovascular System

- Alexander E. Emotional Factors in Essential Hypertension, *Psychosom Med* 1 173 1933
- Connor I. The Psychic Factors in Heart Disease *J A M A* 94 44, 1930
- Gunther I. and Menninger K. A. Intermittent Extrasystole Directly Associated With Emotional Conflict *Bull Menninger Clinic* 3 164 1939
- Katz L. Winton, S. and Melibow, R. Psychosomatic Aspects of Cardiac Arrhythmias *Ann Int Med* 1 27-61 1947
- Gilbert N., Fenn G. Le Roy G. and Holbe, T. Role of Sympathetic Inhibition in the Production of Anginal Attacks *Tr A Am Physicians* 56 219 1941
- Hess I. Relation Ship of the Vegetative Nervous System to Anginal Anxiety *J Nerv & Ment Dis* 104 450 1940
- Menninger K. and Menninger W. Psychoanalytic Observations in Cardiac Disorders, *Am Heart J* 11 10 1930
- Menninger W. C. Functional Cardiovascular Disorders 'Cardiac Neurosis' *Southwestern Med* 21 291 1931
- Saul L. I. Hostility in Cases of Essential Hypertension *Psychosom Med* 1 153 1930
- White I. D. and Craig H. R. Neurocirculatory Asthenia *Arch Int Med* 53 603 1934
- Wittkower L., Rolger T. and Wilson, A. Effort Syndrome *Lancet* 1 531 1941
- Wolfe T. P. Emotions and Organic Heart Disease *Am J Psychiat* 93 681 1936

#### Upper Gastrointestinal System

- Alexander E. and co workers. The Influence of Psychologic Factor Upon Gastrointestinal Disturbances a Symposium *Psychoanalyst Quart* 3 501 1934
- Alexander F. Psychological Aspects of Medicine *Psychosom Med* 1 7 1933
- Bond I. D. Psychiatric Contributions to the Study of the Gastrointestinal System *Am J Digest Dis & Nutrit* 5 452 1935
- Cushing, H. Peptic Ulcers and the Interbrain *Surg Gynec & Obst* 55 1, 19
- Daniels G. E. Neuroses Associated With the Gastrointestinal Tract *Am J Psychiat* 91 521 1934
- Ferenczi S. Materialization in Globus Hystericus In Further Contributions to the Theory and Technique of Psychoanalysis *Internat Psychoanal Library* No 11
- Keller A. D. Protection by Peripheral Nerve Section of Gastrointestinal Tract From Ulceration Following Hypothalamic Lesions *Arch Path* 21 165 1936
- Menninger W. C. Functional Disorders of the Gastrointestinal Tract, the Gastrointestinal Neuroses *Am J Digest Dis & Nutrit* 4 4, 193
- Winkelstein A. One Hundred and sixty nine Studies in Gastric Secretion During the Night *Am J Digest Dis & Nutrit* 1 118 1935
- Wittkower L. Ueber den Einfluss der Affekte auf den Gelfluss *Klin Wchnschr* 7 193 19 5
- Wolf S. and Wolff H. Human Gastric Function ed 2 New York, 1947, Oxford University Press
- Wolff S. and Wolff H. The Gastric Mucosa Gastritis and Ulcer *Am J Digest Dis* 10 23 1943

#### Lower Gastrointestinal Tract

- Alexander F. and co workers. The Influence of Psychologic Factors Upon Gastrointestinal Disturbance a Symposium *Psychoanalyst Quart* 3 501 1934
- Bockus H. Bank J. and Wilkinson S. Neurogenic Mucous Colitis, *Am J M Sc* 176 813, 19 8

Conversion hysteria may produce many bizarre muscular phenomena such as spasticity, paralysis, paresis, spasmodic movement, and so on. Descriptions of these reactions will be found in many psychiatric texts and articles.

## References

### General

- Abraham K. Selected Papers on Psychoanalysis, London, 1927, The Hogarth Press.
- Alexander F. Fundamentals of Psychoanalysis, New York, 1948, W. W. Norton & Co. Inc.
- Alexander F. and French T. M. Studies in Psychosomatic Medicine, New York, 1948, The Ronald Press Co.
- Cannon W. B. Bodily Changes in Pain, Hunger, Fear, and Rage, ed. 2, New York, 1940, The Appleton Co.
- Dunbar I. Emotions and Bodily Changes, ed. 3, New York, 1946, Columbia University Press.
- Dunbar I. Psychosomatic Diagnosis, New York, 1941, Paul B. Hoeber Inc.
- Einichel O. The Psychoanalytic Theory of the Neurosis, New York, 1940, W. W. Norton & Co.
- Freud, S. A General Introduction to Psychoanalysis, Garden City, N. Y., 1947, The Garden City Publishing Co. Inc.
- Freud S. Collected Papers, vols. I-IV, London, 1934, The Hogarth Press.
- Freud S. The Problem of Anxiety, New York, 1936, The Psychoanalytic Quarterly Press and W. W. Norton & Co. Inc.
- Freud S. Three Contributions to the Theory of Sex, New York, 1948, Nervous and Mental Disease Monographs.
- Group for the Advancement of Psychiatry. Report on Problems of Psychotherapy, Circ. Ltr. No. 114, Sept. 30, 1948.
- Halliday J. I. Psychosomatic Medicine, New York, 1948, W. W. Norton & Co. Inc.
- Hartman H. Kris E. and Loewenstein H. M. Comments on the Formation of the Psychic Structure, The Psychoanalytic Study of the Child, vol. II, New York, 1946, International Universities Press.
- Kubie J. S. A Psychological Approach to the Concept of Anxiety, Psychosom. Med. 3, 67, 1941.
- Kubie J. S. Instinct and Homeostasis, Psychosom. Med. 10, 10, 1948.
- Kuntz A. The Autonomic Nervous System, ed. 3, Philadelphia, 1947, Lea & Febiger.
- Levine S. Psychotherapy in Medical Practice, New York, 1943, The Macmillan Co.
- Margolin S. Verbal communication.
- Maserman J. H. Principles of Dynamic Psychiatry, Philadelphia, 1946, W. B. Saunders Co.
- Pavlov I. I. Conditioned Reflexes and Psychiatry (Trans. and Ed. by Gantt W. H.), New York, 1941, International Publishers Inc.
- Weiss L. and English O. S. Psychosomatic Medicine, Philadelphia, 1947, W. B. Saunders Co.
- Witmer, H. I. Teaching Psychotherapeutic Medicine, New York, 1941, The Commonwealth Fund.

### Respiratory System

- Alexander F. and Saul I. Respiration and Personality—Preliminary Report, Psychosom. Med. 2, 110, 1940.
- Binger, C. Psychobiology of Breathing, Ann. Int. Med. 11, 190, 1934.
- Christie R. Some Types of Respiration in Neurosis, Quart. Jour. Med. 4, 421, 1930.
- French T. M. and Alexander F. Psychogenic Factors in Bronchial Asthma, Psychosom. Med. Monograph No. 1, 1941.
- Holmes T. H., Goodell H., Wolf S., and Wolff H. G. Changes in the Nasal Function Associated With Variations in Emotional State and Life Situation, Tr. Am. Acad. Ophth. 51, 449, 1941.

## CHAPTER XVII

### DISEASES OF THE LOCOMOTOR SYSTEM

#### INTRODUCTION

Diseases of the locomotor system include all conditions which interfere with the proper function of the muscles bones joints and ligaments, or periarticular tissues. In addition to these structures many neurogenic conditions may interfere with bodily movement these have been considered under Diseases of the Nervous System. It is seldom that the locomotor system is the site of a local disease. One of few exceptions to this is osteogenic tumors. In general practically all the lesions of muscles bones and joints are dependent upon some systemic or neurogenic disturbance. Many examples might be cited such as the arthritis in rheumatic fever and gonorrheal bacteremia, the bone lesions of scurvy and rickets due to avitaminosis, osteofibrosis cystica resulting from hyperparathyroid function and muscular wasting as found in scurvy, peripheral nerve lesions and chronic debilitating diseases. Therefore many of the important conditions which interfere with locomotion are dealt with in other sections. Although the majority of these lesions are obvious as to their character the fundamental cause is often unknown. It is seldom that one tissue alone is affected, as for instance in a chronic arthritis not only are the periarticular and articular structures affected but there are also found changes in the bones and muscles. Therefore in considering any individual case the symptoms and signs must all be carefully analyzed in relation to the probable primary cause.

#### DISEASES OF THE BONES

Diseases of the bones may be classified under three main headings namely new growths infections and metabolic disturbances. The first are usually dealt with as surgical diseases in that their therapy principally lies in this field. The infections are mainly encountered in tuberculosis syphilis, typhoid fever and pyogenic infections. The osseous tissues proper the medulla or the periosteum may be involved individually or collectively producing an osteitis periostitis or osteomyelitis.

#### Tumors

The following classification of tumors of the bones has been recommended by the American College of Surgeons.

- 1 Tumors related to cartilaginous growth
  - 1 Bone cysts or osteitis fibrosa.
    - A. Solitary, B multiple.
  - 2 Benign giant cell tumor
    - A Typical B variants of giant cell tumor
  - 3 Osteolytic sarcoma
    - A Chondroblastic B osteolytic forms of osteogenic sarcoma

- Da Costa, J M Mucous Enteritis, *Am J M Sc* 89 321 1871
- Groen, Y Psychogenesis and Psychotherapy of Ulcerative Colitis *Psychosom Med* 9 151 1947
- Daniels, G E Treatment of a Case of Ulcerative Colitis Associated With Hysterical Depression *Psychosom Med* 2 276 1940
- Lindemann F Psychiatric Aspects of the Conservative Treatment of Ulcerative Colitis *Arch Neurol & Psychiat* 53 322, 1945
- Manning, G Hall G and Bunting F Vagus Stimulation and Production of Myocardial Damage *Canad M A J* 37 314 1937
- Murray, C D A Brief Psychological Analysis of a Patient With Ulcerative Colitis *J Nerv & Ment Dis* 72 617 1930
- Ross W D Studies of Committee on Ulcerative Colitis Personal Communication
- Sullivan A and Chandler C Ulcerative Colitis of Psychogenic Origin Report of Six Cases *Yale J Biol & Med* 4 779, 1932
- Sullivan A J Emotions and Diarrhea *New England J Med* 214 291 1936
- White, B Cobb S and Jone C Mucous Colitis A Psychological Medical Study of Sixty Cases *Psychosom Med Monographs* No 1 1930

In addition to the osseous lesions there are a number of systemic features which indicate that the disease is not a local one. Bronchitis and emphysema are common and may be explained by the changes in the thoracic cage, also numerous neurologic symptoms and signs such as paralyses, the pain and other sensory disturbances are due to the involvement of the spine. In about 65 per cent of the cases Bence Jones protein is found in the urine. This is a protein with a small molecule and readily passes through the healthy glomerular membrane. It is recognized on heating acidulated urine to 60 C, when a flocculent coagulum appears only to fade away as the temperature approaches to the boiling point. On cooling the cloudiness reappears but again clarifies as about 40 C is reached. In these cases it is customary to



Fig 40—X ray of the skull in a case of multiple myeloma. Note the characteristic appearance of numerous small punched out areas. Compare with Fig 444

find an increased amount of nonprotein nitrogen in the blood. This is not due to urea, uric acid or creatinine nor are there other signs of impairment of renal function. The power of urinary concentration is maintained and the arterial blood pressure is low. The exact cause of this nonprotein nitrogen retention is at present unknown. Examination of the blood reveals no abnormalities unless there be anemia, which distinguishes it from 'Chloroma' (see page 560). Severe secondary anemia, lowered plasma proteins, edema and emaciation occur in advanced cases.

The x ray findings suggest the true nature of the lesion. There will be found varying numbers of round or oval punched areas resembling small cysts in the bones mentioned above (see Figs 440 and 431).

## II Tumors related to precartilaginous and preosseous connective tissue

- 1 Benign osteochondromas or exostoses
  - A Single, B multiple
- 2 Central chondromas or chondromyxomas
- 3 Osteogenic sarcomas containing cartilage or chondromyxosarcoma
  - A Primary, B secondary
- 4 Osteogenic sarcoma with osteoblasts

## III Tumors not primarily of osseous origin

- 1 Ewing's endothelial myeloma
- 2 Multiple myeloma
- 3 Metastatic carcinoma
- 4 Fibrosarcoma.

For a description and discussion of tumors of the bone the reader is referred to textbooks on the practice of surgery. It has been the custom to deal with them in such texts much more fully than in books devoted primarily to medicine. Whether this is altogether advisable is open to argument. The principal excuse for this custom seems to be in the fact that the majority of the lesions are local and cannot, therefore, be considered as systemic disturbances and, further, they are usually amenable to surgical therapy. There are however, several osseous conditions that can with propriety be considered at this juncture.

### Multiple Myeloma

**Synonym**—Kahler's disease

**Definition**—Multiple myeloma is a systemic disease of the bone marrow consisting of sharply defined tumors which replace the medullary tissues and sometimes invade the compact bone.

**Etiology**—The cause of this disease is not known. It is not found in the early decades but occurs with increasing frequency after thirty and reaches a maximum incidence between fifty and sixty.

**Pathological Anatomy**—There is much evidence to suggest that the tumorlike masses arise from a bone marrow element which is not concerned with blood formation. The process begins in the medulla and through invasion of the compact bone reduces this to a mere shell which is easily broken. The contents of these masses appear to be a mixture of leucocyte cells, erythrocytes and fat in a jelly like condition. The most common sites for the lesion are the spine, ribs, cranium and the proximal ends of the femora and humera.

**Symptoms and Signs**—The initial symptom in the majority of cases is intermittent rheumatic pain felt in a variety of places determined by the position of the lesion. It usually radiates to the arms and legs and may have girdle distribution. The onset is insidious and is aggravated by movement. There are violent exacerbations and blessed remissions but the progress is to an agonizing termination. The most severe pain is undoubtedly due to pressure on the spinal roots and the remissions result from tumor regression.

There is skeletal deformity in 60 per cent of the cases from bone destruction leading to sinking of the sternum, kyphosis and pathological fractures which are most frequent in the ribs.



**Prognosis**—The course is uniformly to a fatal termination in about six to twelve months although patients have been reported who have lived for five years

**Treatment**—There is no known specific therapy. As far as possible pathologic fractures should be prevented and when they do occur it must be appreciated that they heal if properly treated and fixation in good position is usually sufficient. Surgical interference for the correction of pressure complications such as lumpectomy for paraplegia is indicated as a temporary measure.

### Chloroma

See page 960 under Acute Leucemia

### Osteitis Fibrosa Cystica

See page 964 under Hyperparathyroidism

### Metastatic Carcinoma

Metastatic carcinoma of the bones presents an extremely variable group of symptoms. "Rheumatic" pain is the outstanding symptom. This may be localized when a single focus is present (50 per cent) which is usually in the end of one of the long bones at the site of the entrance of the nutrient vessel. On the other hand they may be without number when the pain will be diffuse and its multiplicity makes it impossible of accurate location. Under the latter conditions there is usually an increased oxygen consumption and Benedict's protein may be found in the urine (see page 1206).

The principal sources of bone metastases are primary carcinoma of the prostate, breast, thyroid and hypernephroma which account for over 75 per cent. They may arise however from many other sources.

### Metabolic and Developmental Disorders

Many of the pathological conditions of the bones due to metabolic and developmental disorders have already been referred to in diseases of nutrition, ductless glands and the reticulo-endothelial system. A summary of these disorders will be found as follows:

#### Asthenia is

- Rickets (page 99)
- Renal rickets (page 1081)
- Osteomalacia (pregnancy) (page 803)
- Curry (page 95)

#### Hyperparathyroid Function

- Osteitis fibrosa cystica (page 964)

#### Pituitary Function

- Acromegaly (page 893)
- Gigantism (page 89)
- Dwarfism (page 906)
- Pituitary basophilism (page 896)

**Diagnosis**—The diagnosis rests upon the x ray findings and the presence of Bence Jones protein in the urine. It is to be distinguished from metastatic carcinoma in the skeleton. At times this may be impossible without a biopsy as in both conditions the x rays may be identical and Bence Jones protein may be present. A primary tumor and metastases in the lung (rare in myeloma) are in favor of carcinomatosis as is also a single tumor. But only



**Fig. 431**—X ray of the humerus and shoulder girdle in a case of multiple myeloma. Note the characteristic punched out areas particularly in the humerus and ribs. Compare with Figs 388 and 445.

a single area may be found in myeloma and multiple bone metastases are found in carcinomatosis. An increased oxygen consumption (BMR) is in favor of the latter.

Other conditions to be distinguished from myeloma are chloroma (page 560), osteitis fibrosa cystica (page 964) and osteitis deformans (page 1222). A thorough examination readily reveals the true diagnosis.

is flattened, the lower jaw is prominent, and the tongue and lips are thickened. There is a real as well as an apparent enlargement of the head. The trunk is normal in size and proportion while the extremities although well formed are short which is particularly apparent in the legs. Instead of the center of the stature being at the symphysis pubis it is nearer the xiphoid (Fig. 432).

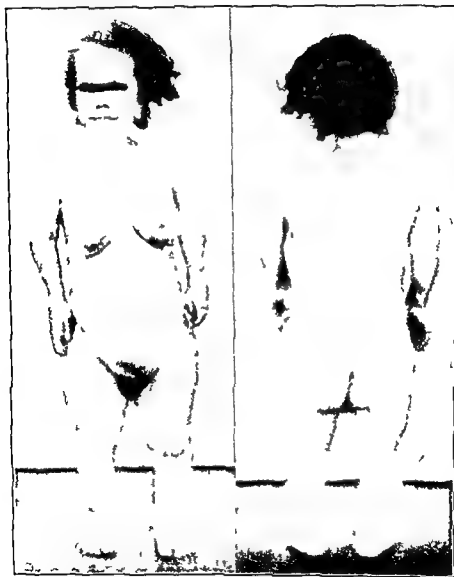


FIG. 432

FIG. 433

Fig. 432—Front view photograph of a female with acromegaly, aged thirty-seven and a half months pregnant.

Fig. 433—Rear view photograph of the same patient as shown in Fig. 432.

The hands are small and the fingers tapering, all of them being of about equal length and when extended appear like the spokes of a wheel known as the main en trident. The muscles of the extremities appear to be hypertrophied or abnormally developed but their physical strength is not increased. The skin

**Hereditary**

- Achondroplasia (page 1210)
- Hereditary deforming chondrodysplasia (page 1213)
- Multiple congenital enchondrosis (page 1214)
- Osteogenesis imperfecta (page 1215)
- Osteopetrosis—Albers-Schönberg's disease (page 1216)
- Milbright's syndrome (page 1219)

**Systemic Diseases**

- Hypertrophic osteoarthropathy (page 1220)

**Unknown Causes**

- Hand-Christian syndrome (page 1229)
- Osteitis deformans—Paget's disease (page 1227)
- Microcephaly—Congenital ossia (page 1227)
- Acrocephaly—Steep head (page 1227)

The diseases of the bones that have not been dealt with elsewhere are principally confined to those that have a hereditary or unknown background and most of these come under the former category. In fact it is one of the interesting observations in clinical medicine that it is not unusual for a familial or constitutional direction to be given to many of the diseases of the bones, joints and muscles. They do not, however, follow the general rules of inherited characteristics but are more inclined toward a scattered accidental occurrence. The more important of these diseases are achondroplasia, hereditary deforming chondrodysplasia, osteogenesis imperfecta, and with a suggestive familial tendency, osteitis deformans.

**Achondroplasia**

**Synonym**—Chondrodystrophia fetalis

**Definition**—Achondroplasia is a form of dwarfism due to arrested development of the long bones of the extremities resulting from a perversion of normal endochondral ossification. There have been three forms described: chondrodystrophia malacia in which the lesion is a softening of the epiphyseal cartilages, chondrodystrophia hypoplastica, where there is an abortive cartilaginous growth and chondrodystrophia hyperplastica, where the epiphyseal cartilage overgrows and leads to outward enlargement.

**Etiology**—Congenital and hereditary factors play a dominant role in the causation of this disease. A number of achondroplastic dwarfs may be found in one family, being more common in males than in females. It has been attributed to an abnormally small amnion leading to increased hydrostatic pressure which is supposed to cause a dystrophy of the original bone cartilage. Another suggestion has been that it is related to cretinism, but both these theories at the best must be considered as speculative.

**Symptoms**—The majority of achondroplasties are stillborn having developed to a fetus between the seventh and ninth months. The death rate of those that come to term is high in the first six months of life, but after this time they do not show any abnormal impairment of their general health. Skeletal abnormalities at birth remain unaltered. The infant is short, usually about three fifths to four fifths the normal length, the bridge of the nose

thickened over the whole body, and about the joints it may appear in folds as if it were too long for the shortened bones. Mentally they are quite alert and both sexes are likely to exhibit increased sexual capacity and the females are expected to be prolific.

The x rays of the limbs are unique, the long bones being shortened, thickened and dense. The line of ossification is irregular and defective. The epiphyses show a sudden expansion as compared to the shafts (Fig 434). There is a type of achondroplasia in which the shafts of the bones appear softer than normal and as a consequence may undergo considerable distortion. An example of such is seen in Fig 435.

**Pathological Anatomy**—The anatomical changes appear to be the findings expected from the x rays. The epiphyses are hypertrophied and the shafts of the bones show active periosteal proliferation, while the endochondral ossification is absent. There is, however, a complete aplasia of the long bone development while the epiphyses are abnormally enlarged.

**Diagnosis**—The diagnosis is made without difficulty as there is no other disease which simulates its peculiar characteristics.

**Treatment**—There is no known treatment.

### Multiple Cartilaginous Exostoses

**Synonym**—Hereditary deforming chondrodysplasia

**Definition**—Multiple cartilaginous exostoses is a condition where numerous exostoses of congenital origin occur chiefly toward the ends of the long bones.

**Etiology**—This condition may occur in members of the family of the same generation and in different generations but it does not follow the Mendelian laws. They are supposed to be due to a developmental anomaly of the epiphyseal cartilage and by others are considered as misplaced cartilaginous tissue which in time forms true bone.

**Symptoms**—There are no objective or subjective symptoms unless they interfere with local function. The exostoses are usually recognized on palpation or by x ray examination. They are always multiple and may number scores (even to more than one hundred) and are most commonly found at the ends of the long bones, the ribs, vertebrae and pelvis. If they occur in the legs or forearms the bone principally affected does not grow as much as its companion and therefore a deformity may develop. The x ray pictures show the position and shape of the exostoses and also demonstrate that it communicates directly with the medullary cavity (see Fig 436).

**Pathological Anatomy**—The outer surface of the exostoses is formed by perichondrium beneath which is cartilage and within this sheath cancellous bone may be found. Occasionally sarcomatous changes occur. The other unusual features are accidental such as fractures, pressure on nerve trunks or even on the spinal cord when the vertebrae are involved, erosion of blood vessels producing aneurysms, etc.

**Diagnosis**—This is made with certainty by x ray examination.

**Treatment**—If they cause pain from pressure or interfere with function they should be removed by surgical methods.



Fig 434—X ray of the legs in a case of achondroplasia



Fig 435—X ray of the arm in a case of achondroplasia.

**Pathological Anatomy**—The anatomical change is found at the junction of the diaphysis with the metaphysis where a protruding mass of hyaline cartilage is found

**Diagnosis**—When the condition is multiple, there is little difficulty in recognizing its true condition, but if single it may be confused with fibrocytic diseases chondroma a giant cell tumor or other local bone lesion

**Prognosis**—It does not affect the general health and is only of importance when the tumors interfere with skeletal function

**Treatment**—There is no treatment known which affects the general course of the disease If the tumors interfere with function they should be removed



Fig 42 —X ray of a hand in a case showing multiple enchondromas (From the Children Memorial Hospital Montreal)

### Osteogenesis Imperfecta

**Synonyms**—Fragilis ossificans, osteopathyrasis fragilitas ossium Lobstein's disease

**Definition**—This is a rare disease of the bones which is characterized by great fragility and numerous fractures usually recognized in infancy and childhood



FIG 436 — X ray of the left fore arm in a case of multiple cartilaginous exostosis (From the Montreal Neurological Institute)

### Multiple Congenital Enchondroses

**Synonyms** —Dyschondrioplasia, multiple enchondromata

**Definition** —There is an abnormal growth of bone and cartilage in the growing end of a bone which may be either single or multiple

**Etiology** —It is a rare congenital disease of unknown cause, but appears to be due to a congenital abnormality of the epiphyseal cartilage

**Symptoms** —This lesion is irregularly distributed but is most frequently found in the phalangeal and metacarpal bones. The next most frequent site is the long bones of the extremities. It is recognized either by a palpable mass or through localized lack of development. The x ray pictures reveal what appear to be cartilaginous protrusions or masses which contain irregular areas of calcification (see Fig 437)



tures. The bone shadow is extremely thin and often can hardly be distinguished from the surrounding soft parts. This is accentuated by the increased density where fractures have occurred. The medullary cavity when seen is irregular and dilated, the epiphyseal line is straight and the cartilage thin. With such profound changes in the structure of the bones it would be expected that definite changes in the metabolism of calcium phosphorus magnesium or potassium would be detected but the results so far reported are conflicting. In fact the results have been within normal limits in the more carefully conducted observations except perhaps for a slight negative calcium balance. The long bones are principally affected as represented by the number of fractures but fractures of the bones of the skull have also been reported.

**Pathological Anatomy**—The anatomical changes consist of an extreme fragility due to thinning, particularly of the shafts of the long bones and ribs. The epiphyses are normal and there is no increased flexibility of the bones the whole lesion being confined to an almost paper thinness of the bony cortex. The periosteum is however thin and shows little or no activity, the medullary canal is dilated with fibrous metaplasia of the marrow.

**Diagnosis**—The diagnosis rests upon the x ray appearance of the shafts of the bones and the occurrence of multiple fractures. It does not bear any resemblance to rickets, scurvy or congenital syphilis.

**Prognosis**—Most fetuses so afflicted die *in utero* or shortly after birth. If they survive the first year of life the prognosis as to life is good but increasing disability occurs during childhood from the numerous fractures. During the second decade these become less frequent and after the twentieth year they rarely occur.

**Treatment**—Care of the child to prevent fractures in fact keeping it actually as well as metaphorically wrapped in cotton wool with a high vitamin diet to prevent any deficiency disease of childhood is the main objective. Many drugs have been advocated but all are useless. Archibald has attempted to prevent fractures by artificially splitting the bones longitudinally and thus producing a callous splint to the bones through their whole length. It is a tedious procedure but if it can be carried out has a reasonable basis.

### Osteopetrosis

**Synonyms**—Marble bones, chalk bones, Albers-Schönberg's disease, osteosclerosis fragilis generalisata, congenital osteosclerosis and hyperostotic osteopathy.

This is a comparatively rare disease of the bones which has a definite hereditary background. It may be present at birth or become manifest during childhood or even later in life. It is a progressive disease and affects the skull as well as the long bones. The sclerosis or petrosis may first appear either at the end or in the middle of the shaft and progress centripetally or centrifugally.

The patient first comes under observation either for symptoms referable to the cranium or the cranial nerves such as hydrocephalus, blindness due to

**Etiology**—It is a congenital disease of the skeleton apparently dependent upon a nutritional abnormality during fetal life, the exact cause of which is unknown. It occurs equally in both sexes.

**Symptoms**—The signs and symptoms of this disease are confined entirely to the bones which are extremely fragile. The subsequent deformities are due



Fig. 438—X ray of the legs in a case of osteogenesis imperfecta, showing the pincer lines of the cortex and enlargement of the medullary cavity, and the fracture of both femurs.

to the fractures which unite normally although frequently in gross malposition (Fig. 438). The callous formation is normal even at times excessive; this may give to the bones an irregular beaded character best recognized by the x rays. The x ray appearance of the bones is quite distinctive. The remains of numerous fractures are usually obvious whether in proper alignment or leading to gross deformities, although the bones are of normal length if not shortened by frac-

There has been much divergence of opinion regarding the abnormal texture of the bones which is undoubtedly due to the various stages of the disease or accidental samples of bone which have been examined. There is first a period of rarefaction followed by increased calcium deposit which is of a chalky nature, but eventually the bone becomes intensely hard from osteopetrosis, and at this time it is compared with marble.

There has been much discussion also of the biochemical changes in the bones, but as yet their cause is unknown. It has been suggested by some that they may represent an osteoblastic stage of hyperparathyroidism, when the activity of the parathyroids causes deposition rather than metabolism of calcium but the evidence to substantiate this is quite inconclusive.

As stated above the disease is progressive but it may be slowly so and individuals sometimes reach adult life without great inconvenience.

Treatment so far has been of no avail.

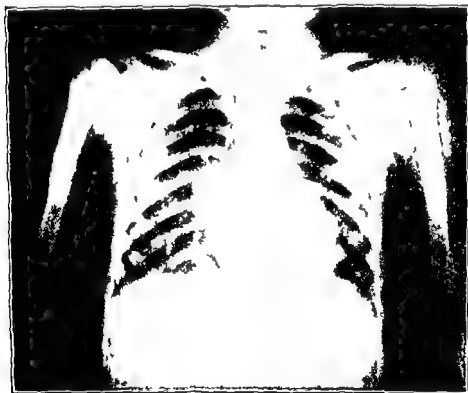


Fig. 440.—X-ray of the daughter of the patient shown in Fig. 429, showing a marble bone formation at the upper end of the humerus. (Courtesy of the late Dr. A. Howard Fries.)

### Fibrous Dysplasia

**Synonym** — Albright's syndrome

**Definition** — A rather rare congenital fibrous replacement of the bones and sometimes any or all of the following: premature sexual development, pigmentation of the skin, hyperthyroidism and other more uncommon extra-skeletal disturbances.

optic atrophy, deafness, or some other cranial nerve palsy, or, on the other hand for pronounced anemia. The first group of symptoms are due to the encroachment of the sclerosing bone upon the various cranial foramina (Fig 422). As this is irregular in distribution the resulting symptoms may be most bizarre. The anemia results from the gradual obliteration of the medullary canal. It is usually of the myelophthisic type or of the hyperchromic type. Overactivity of the uninvolved bone marrow is indicated by an increase of reticulo-cytes and normoblasts in the peripheral circulation. In time a true aplastic



Fig 439—X-ray of a skull of a patient (marbled bone) of Albrecht's disease (case C) showing the dense character of the vertebrae and the pelvic bones. The patient was pregnant at the time. The fetal vertebrae are well seen. (Courtesy of the late Dr. A. Howard Pirie.)

anemia appears. In addition to the anemia there is also an enlargement of the liver, spleen and lymphatic glands which is considered compensatory. There is also clubbing of the fingers and spontaneous fractures through areas of bony rarefaction are not uncommon. There is retarded skeletal growth which has been suggested by some as due to a pituitary origin through involvement of this gland in the bony changes at the base of the skull. There is delayed eruption of the teeth and frequently dental caries. The true nature of the disease is recognized by X-ray. (See Figs 439 to 442.)

of the terminal phalanges there may also be a thickening of the bones of the forearms, legs, and more rarely the femur and humerus, and slight evidence may be found in the flat bones. It begins in the diaphysis as a thickening of the shaft being due to the irregular deposit of new bone under the periosteum.



Fig. 441.—X ray of the leg of a case of marble bones where the lesion began in the shafts extending toward the epiphyses.

In advanced cases this appears by x ray as a shell surrounding the original shaft. There is also a thickening of the neighboring soft tissues but the musculature atrophies. This cannot be considered as a separate disease as it is always secondary to some visceral lesion. It is rare that it assumes pronounced proportions. There are remissions and exacerbations of the condition parallel with such in the original disease. This is particularly notice

**Etiology**—This is undoubtedly a congenital disease and affects females much oftener than males.

**Symptoms**—The symptoms are inherent in the skeletal and systemic disturbances as they appear and will therefore be considered under the following headings:

**Bones**—The lesion in the bones is a fibrous replacement in isolated areas with apparently normal bone elsewhere. One or many bones may be the site of the lesion but there is a predilection to it being unilateral. These fibrous areas contain spindle cells with an indistinct cytoplasm and a pale nucleus. The x-ray reveals well defined areas of rarefaction. Spontaneous fractures occur. Calcium and phosphorus metabolism is normal.

**Pigmentation**—This may not be present but if it is it varies considerably in area up to large patches chiefly over the sacral and lumbar regions, buttocks and back of the neck. The color shades from a pale fawn to a deep brown. It is due to an increased number of melanoblasts and melanin in the skin and corium.

**Premature Sexual Development**—Menstruation may start as early as two years of age and continue to be profuse but with irregular periods of duration and interval. Conception has been reported as early as five years.

**Hypothyroidism**—This shows the usual symptoms and signs and is unusual solely on account of the early age incidence.

The diagnosis in the complete form offers no difficulty. In cases with bone lesions only, it may be confused with osteitis fibrosa cystica but the mineral metabolism clears the picture.

The prognosis is fairly good as to life.

**Treatment** is of no avail except in solitary cysts of the bone which may be removed and bone chips may be placed in the cavity.

### Other Hereditary Bone Diseases

**Hereditary Arthrodysplasia and Dystrophy of the Nails**—Absence of the patella and congenital dislocation of the head of the radius. There may also be in association or independently absence or dystrophy of the nails.

**Morquio's Disease**—A familial osseous dystrophy showing delay in development rarefaction and deformity of the bones of the limbs with occasionally cranial changes leading to optic atrophy.

**Hypertelorism**—A familial tendency to excessive development of the lesser wings of the sphenoid bones leading to wide separation of the orbits and often an associated mental defect.

### Hypertrophic Osteoarthropathy

**Synonyms**—Marie's disease Hippocratic fingers

**Definition**—In its entirety this is a comparatively rare disease. It is most frequently manifested by the clubbing of the fingers found in chronic pulmonary lesions, subacute bacterial endocarditis and chronic anoxemia as in the cyanotic forms of congenital heart disease. In addition to the enlargement

more frequently afflicted than females. The cause has been attributed to almost every possible etiological factor that could be thought of, ranging all the way from bacterial infection, cancer, trauma, neurogenic factors and endocrine disorders. There are only two facts of importance which might have a bearing on the etiology, namely, a familial history in about 30 per cent of the cases, and an unusually large incidence of arteriosclerosis or arterial atheroma. Whether or not the latter is a contributing cause or an effect is unknown.



FIG. 443.—X-ray of the lower half of the leg from an early case of hyperostosis. The thickening of the shaft of the tibia is characteristic of the disease. The thickening is most marked in the middle of the shaft of the tibia and posterior border of the fibula.

**Symptomatology**—The onset of the disease is so insidious that it is impossible to date its exact time, and the first indication of its presence is usually found in a distortion of some single bone, such as the skull or one of the extremities. It may remain arrested in this stage or gradually progress to involve all the bones of the skeleton. The head and mandible show progressive enlargement; the spine gradually becomes bowed and rigid, while the arms and legs also show bowing and great thickening. The shoulder girdle and the pelvis gradually enlarge until they assume massive proportions. The body is bent forward in order to maintain equilibrium, and this posture with distortion of the skeleton leads to a conspicuous reduction in stature.

With the gradual progression and the skeletal changes, pain soon develops. It varies greatly in intensity and character. At times it is dull and aching

able when it is associated with bronchiectasis, pulmonary tuberculosis, or amebic dysentery (see Fig 44b)

The diagnosis is comparatively easy, and the treatment is that of the primary disease



Fig 44 —X ray of the skull in the same case as in Fig 44a showing the increased density particularly of the base which led to optic atrophy and deafness

### Osteitis Deformans

**Synonym**—Paget's disease

**Definition**—*Osteitis deformans* is a chronic disease of unknown origin affecting the bones. There is extensive rarefaction and condensation which lead to enlargement and irregular deformities both of the long and flat bones.

**Etiology**—The exact cause of this disease is unknown. It usually appears between the ages of thirty and fifty, seldom before or after, and males are



The x ray appearance of the skeleton is quite distinctive. The calvarium becomes progressively thickened and gives the appearance as if crinkling hairs were distributed throughout. The vertebrae are enlarged and appear like building blocks with absorption of their centers. The long bones and ribs are much broader than normal and show definite deformities. All these bony changes are due to the progressive condensation and absorption. There is no evidence that there is a calcium or phosphorus loss but rather a redistribution.

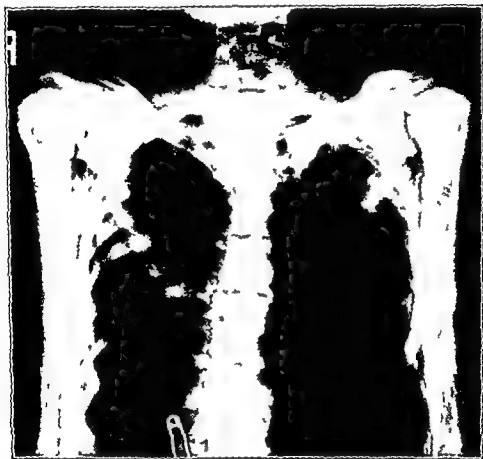


Fig 445—X ray of the upper arms, shoulder girdle and chest of the same case as in Fig. 444 showing irregular distribution of calcification and absorption particularly in the humeri. Note the dense building block appearance of the vertebrae.

The analysis of whole bone shows normal proportions but if different parts of the bone are analyzed there may be found either an increase or a decrease of calcium or phosphorus depending upon the site from which the samples are taken (Figs 444 to 446).

**Pathological Anatomy**—The anatomical changes are chiefly to be found in the skull and long bones although the shoulder girdle, pelvis and ribs are also involved in advanced cases. There is evidence of progressive absorption or reduction of one part of the bone, and a condensation or ossification in other parts, the latter particularly taking place in the periosteum, hence the

and at others paroxysmal and violent. It is exaggerated on standing or walking, and is usually worse at night. The bones are tender, particularly over the anterior borders of the tibia where there may develop an associated periostitis. When the disease is well established, fractures may be spontaneous or follow slight trauma. Union is usually unimpaired.



Fig. 444.—X ray of the skull in a case of osteitis deformans or Paget's disease showing the characteristic areas of absorption and calcification. Note particularly the density of the base. This case required trephining to relieve symptoms from arachnoid degeneration causing cerebral pressure.

The musculature also shares in the general condition. There are cramps and the muscles gradually atrophy, leading to extreme fatigue and weakness. An important feature in the progressive development of the disease are cardiovascular lesions. Arteriosclerosis is practically always present and of an advanced degree which in time leads to cardiac failure, cerebral hemorrhage or infarctions, and symptoms of intermittent claudication. Osteosarcoma is not an infrequent development, as are also degenerative and chronic infectious diseases of the lungs, such as chronic bronchitis, tuberculosis, and emphysema.

The x ray appearance of the skeleton is quite distinctive. The calvarium becomes progressively thickened and gives the appearance as if curling hairs were distributed throughout. The vertebrae are enlarged and appear like building blocks with absorption of their centers. The long bones and ribs are much broader than normal and show definite deformities. All these bony changes are due to the progressive condensation and absorption. There is no evidence that there is a calcium or phosphorus loss but rather a redistribution.

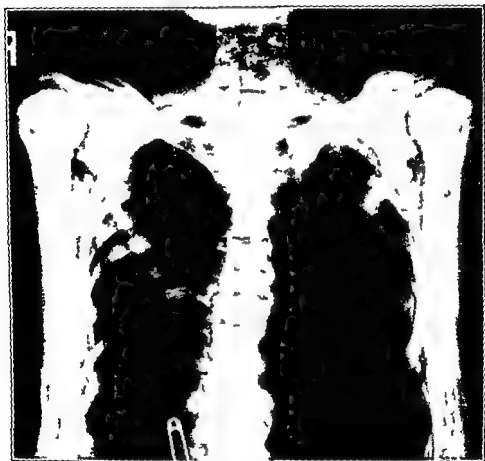


Fig. 44.—X ray of the upper arms, shoulder girdle and chest of the same case as in Fig. 444 showing irregular distribution of rarefaction and density, particularly in the humeri. Note the dense "building block" appearance of the vertebrae.

The analysis of whole bone shows normal proportions but if different parts of the bone are analyzed there may be found either an increase or a decrease of calcium or phosphorus depending upon the site from which the samples are taken (Figs. 444 to 446).

**Pathological Anatomy**—The anatomical changes are chiefly to be found in the skull and long bones, although the shoulder girdle, pelvis and ribs are also involved in advanced cases. There is evidence of progressive absorption or reduction of one part of the bone and a condensation or ossification in other parts, the latter particularly taking place in the periosteum, hence the

and at others paroxysmal and violent. It is exaggerated on standing or walking, and is usually worse at night. The bones are tender, particularly over the anterior borders of the tibia where there may develop an associated periostitis. When the disease is well established, fractures may be spontaneous or follow slight trauma. Union is usually unimpaired.



Fig. 444.—X ray of the skull in a case of osteitis deformans or Paget's disease showing the characteristic areas of absorption and calcification. Note particularly the density of the base. This case required trephining to relieve symptoms from sarcomatous degeneration causing cerebral pressure.

The musculature also shares in the general condition. There are cramps and the muscles gradually atrophy, leading to extreme fatigue and weakness. An important feature in the progressive development of the disease are cardiovascular lesions. Arteriosclerosis is practically always present and of an advanced degree which in time leads to cardiac failure, cerebral hemorrhage or infarctions, and symptoms of intermittent claudication. Osteosarcoma is not an infrequent development as are also degenerative and chronic infectious diseases of the lungs, such as chronic bronchitis, tuberculosis and emphysema.

**Paget's disease** it is only a superficial resemblance and a positive Wassermann usually indicates in the former the proper diagnosis. Osteomalacia occurs usually in young women and there is deformity with little increase in size atrophy being more prominent than hypertrophy. Osteitis fibrosa cystica may give a clinical appearance of bony enlargement but this is due to fibrous metaplasia. Cysts are more prominent and fractures more frequent while the skull usually escapes. The two differences are quite distinctive.

**Prognosis**—The patient seldom dies of osteitis deformans unless from progressive cachexia. Cardiac and vascular lesions malignant disease and pulmonary tuberculosis are the most common causes of death. The disease however is essentially a chronic one and finally may render the victim a complete cripple. It is not unusual for the disease to become quiescent or arrested and all symptoms disappear leaving the established deformities. Cases have been reported where improvement has occurred.

**Treatment**—There is nothing that can be done in a specific way to arrest the disease. There have been reported isolated cases that seem to respond favorably to a variety of so called cures but there is nothing to suggest that these were not mere coincidents. Orthopedic procedures may be necessary to improve function but these are symptomatic measures.

### General Hyperkeratosis of the Skull

**Synonyms**—Megaloccephaly leontiasis ossis

**Definition**—This is a rare disease characterized by great increase or hyperostosis of all the bones of the skull including the mandible. This growth may be either eccentric or concentric. The overgrowth encroaches upon the cerebral cavity and the bony canals being particularly prominent in the orbits and accessory sinuses. The texture of the bone is extremely hard resembling ivory. It is rare that other bones of the skeleton are involved. Irregular growth or exostoses do not occur.

**Symptoms**—The symptoms are bizarre as they are made up of the results of cerebral nervous and vascular pressure. The principal ones are headache and exophthalmos but there may be also cranial nerve palsies insomnia mental disturbances even to insanity and convulsions. Pressure on the veins produces a greater effect than that on the arteries therefore there may be superficial varicosities and signs of intracranial vascular enlargement due to venous stasis. The cause is quite unknown although it is more frequent in females than in males.

**Diagnosis**—The diagnosis is usually quite easy except in the earliest stages. It must be differentiated chiefly from acromegaly and Paget's disease. The course is insidious and prolonged usually lasting from thirty to forty years. Occasionally it may become quiescent. There is no treatment known and when intracranial pressure is sufficiently severe decompression is necessary.

### Acrocephaly

**Synonyms**—Oxicephaly tower head steepie head

**Definition**—This is an unusual disease in which there is a progressive upward enlargement of the cranium as if it were being pulled up to a point

progressive enlargement of the bony diameters. This is irregularly distributed and therefore on section shows a varied appearance. Cysts are rare and do not assume large dimensions.

**Diagnosis**—There is little difficulty in differentiating this disease from other bony lesions. It may be confused with acromegaly, osteoporosis senilis, osteomalacia, syphilitic periostitis or sabre shin, osteitis fibrosa cystica, and



Fig. 446.—X-ray of the lower half of the femora and upper ends of the tibia of the same case as in Fig. 444 and 445.

the adult manifestations of severe infantile rickets. There are, however, particular points about all of these that can easily differentiate them from osteitis deformans. In acromegaly the calvarium and long bones are not affected, osteoporosis is seen in the later decades and is an atrophy rather than a deformity. The sabre shin of syphilis and the boomerang shin of Australia and New Guinea are found only in the tibia and although here it may simulate

Paget's disease, it is only a superficial resemblance and a positive Wassermann usually indicates in the former the proper diagnosis. Osteomalacia occurs usually in young women and there is deformity with little increase in size atrophy being more prominent than hypertrophy. Osteitis fibrosa cystica may give a clinical appearance of bony enlargement but this is due to fibrous metaplasia. Cysts are more prominent and fractures more frequent while the skull usually escapes. The x-ray differences are quite distinctive.

**Prognosis**—The patient seldom dies of osteitis deformans unless from progressive cachexia. Cardiac and vascular lesions malignant disease and pulmonary tuberculosis are the most common causes of death. The disease however is essentially a chronic one and finally may render the victim a complete cripple. It is not unusual for the disease to become quiescent or arrested and all symptoms disappear leaving the established deformities. Cases have been reported where improvement has occurred.

**Treatment**—There is nothing that can be done in a specific way to arrest the disease. There have been reported isolated cases that seem to respond favorably to a variety of so called cures but there is nothing to suggest that these were not mere coincidents. Orthopedic procedures may be necessary to improve function but these are symptomatic measures.

### General Hyperkeratosis of the Skull

**Synonyms**—Megalopcephaly leontiasis ossia

**Definition**—This is a rare disease characterized by great increase or hyperostosis of all the bones of the skull including the mandible. This growth may be either eccentric or concentric. The overgrowth encroaches upon the cerebral cavity and the bony canals being particularly prominent in the orbits and accessory sinuses. The texture of the bone is extremely hard resembling ivory. It is rare that other bones of the skeleton are involved. Irregular growth or exostoses do not occur.

**Symptoms**—The symptoms are bizarre as they are made up of the results of cerebral nervous and vascular pressure. The principal ones are headache and exophthalmos but there may be also cranial nerve palsies insomnia mental disturbances even to insanity and convulsions. Pressure on the veins produces a greater effect than that on the arteries therefore there may be superficial varicosities and signs of intracranial vascular enlargement due to venous stasis. The cause is quite unknown although it is more frequent in females than in males.

**Diagnosis**—The diagnosis is usually quite easy except in the earliest stages. It must be differentiated chiefly from acromegaly and Paget's disease. The course is insidious and prolonged usually lasting from thirty to forty years. Occasionally it may become quiescent. There is no treatment known and when intracranial pressure is sufficiently severe decompression is necessary.

### Acrocephaly

**Synonyms**—Oxycephaly tower head steeple head

**Definition**—This is an unusual disease in which there is a progressive upward enlargement of the cranium as if it were being pulled up to a point

like a bell tent, and in so doing the supraorbital and temporal ridges and the malar and maxillary prominences are flattened, with decreased volume of all the paranasal sinuses (Fig 447). The whole expression is one of vacuity except for the exophthalmos which is constant and gives to the face a most startlingly absurd appearance. This is due to the progressive shallowness of the orbital cavities. It may be impossible to close the eyes and in consequence keratitis and conjunctivitis occur. There is also optic atrophy with engorgement of the veins, and errors of refraction are constant. Headaches, vomiting, and other signs of intracranial pressure are common. Convulsions have been reported in children. This abnormality does not seem to influence the length of life. Blindness and deafness are frequent sequelae.

**Treatment**—There is no treatment known which has any effect on its progress, although craniat decompression may sometimes be necessary.



Fig 44.—X ray of the skull in a case of acrocephaly. Note the obliteration of the suture, conspicuous evolutonal marking short and deep frontal and temporal fossae and the enlargement of the sella from pressure. Trephining was necessary to relieve symptoms (From the Montreal Neurological Institute)

## DISEASES OF THE MUSCLES

### Introduction

One of the most common complaints met with in general practice is pain in the limbs, variously attributed by the patient to the muscles, bones, ligaments, and nerves. It may follow exposure to cold, unusual exercise, trauma, or be associated with changes in barometric pressure and often forms a group of prodromata to infections which may eventually culminate in a severe spe-



cific disease or a fleeting upper respiratory infection. The classification of these vague pains and aches is almost an impossible task. There is no doubt that some of them can be definitely attributed to either local or general intoxication, but that they are due to a localized action of bacteria seems problematical. Those due to trauma are quite easily explained, and it is probable that those following unusual exertion are due to muscle fatigue and local capillary circulatory disturbances with possible local accumulations of lactic acid or other products of muscle metabolism. It is well known that they are best treated by a continuation of muscular activity. Another common cause which is too frequently overlooked is muscular tension the result of maintaining an unusual position. A good example of this is pain in the muscles at the back of the neck spreading over the shoulders due to holding the head in a tense position through maladjustment of bifocal or other types of complicated eye glasses. There seems little doubt that many cases of lumbar pain are due to bad static posture as are pains in the lower legs the result of flat feet. The search for the cause of these discomforts is divisible into two lines of investigation. If the pain remains local and constant in distribution it is reasonable to surmise that the cause is local. If on the other hand the pain be more diffuse and intermittent it is to be expected that the cause will be of a systemic character. It is unwise to give a dogmatic diagnosis until a careful search of the cause has been carried out and all possible factors have been analyzed. Although the pain or ache may seem insignificant in itself it is often the first manifestation of a serious local or systemic disease as for instance pain low in the back may be due to carcinoma of the prostate or rectum while vague fleeting pains in the thighs may indicate pressure on the lumbar nerve roots. On the other hand a searching general examination including many laboratory procedures would not seem justified in every vague ache or pain. It is in such cases that the acumen of the clinician is of the greatest value to the patient.

When the pain is localized a careful examination may reveal points of tenderness either in the subcutaneous or deeper tissues, a sense of resistance or rigidity in the muscles or perhaps the patient complains of a definite radiation. These findings immediately suggest a local subcutaneous lesion or a muscle spasm which may be due to a variety of causes or third some condition which is producing local nerve or root irritation and hence the radiation over its distribution. If on the other hand the discomfort is more diffuse and changes from hour to hour and day to day the cause is usually to be found in some far distant area and if unusual exercise and signs of a general infection suggesting the onset of some systemic disease can be eliminated a thorough search must then be made for some focal source of infection or intoxication. Much harm has resulted from dismissing such symptoms too lightly. The patient receiving little sympathy or attention is likely to seek relief from one of the irregular cults or after silently suffering for a space of time returns in desperation for relief and the cause is now obvious but much time has been lost when treatment can do the most good.

Out of this indefinite group of symptoms there crystallizes a number of conditions which may be labeled by many synonyms such as myalgia, fibrositis,

panniculitis, lumbago, muscular rheumatism, etc. Some of these when applied in a strict sense have a reason for their existence, but unfortunately they are used so loosely that they may mean something or nothing. If they are applied in their strict pathological sense, a *fibrositis* would mean a local or general inflammation of the fasciae, muscle sheaths, ligaments, aponeuroses and tendons. Such cases are not unusual. Their general symptomatology is pain, 'stiffness of the joints' and muscular weakness. On examination localized tender areas may be found which also give the impression to the palpating finger of local areas of induration.

*Myositis* strictly means an inflammation of the muscles, and *panniculitis* an inflammation of the subcutaneous fatty tissues. Where *fibrositis*, *panniculitis*, and *myositis* begin and end or when they are all part of a local lesion is difficult to determine. Painful nodules may be palpated in all of them. They are all aggravated by muscular movement. If not due to a local cause such as trauma, they all have a tendency for remissions and exacerbations unless the original cause is removed. Local disturbances of this nature have given rise to a nomenclature which has implied definite diseases and is used in such not only by the laity but also by the profession. In this category may be placed neuralgias, pleurodynia, torticollis, lumbago, indurative or nodular headache, sciatica, etc. It cannot be denied that some of these by their local persistence may in time lead to local anatomical changes and may be most intractable to therapeutic measures, but this does not remove the possibility that in their earliest stages they could have been cured if they had been taken with sufficient seriousness and the local or general cause sought and removed.

There are in addition to these vague signs and symptoms, certain well defined lesions of the muscles and associated tissues of which the following are the most important:

### Primary Suppurative Myositis

**Definition**—This is an acute inflammation of the muscle which may be either single or multiple, and has associated signs of acute infection.

**Incidence**—It is a comparatively rare disease in North America, and has been most commonly described in Japan and tropical Africa where it goes by the name of *myositis purulenta tropica*.

**Etiology**—It is found in both sexes and at all ages and is usually attributed to an infection by the *Staphylococcus aureus*, the portal of entry of which is not constant.

**Symptoms**—The onset is sudden with a chill and pyrexia. This is also accompanied by the usual general symptoms of infections such as malaise, anorexia, headache, generalized pains and sweating. In a short time localized areas of swelling, tenderness and induration are found in the muscles involved. These may be isolated or occur in groups which may eventually coalesce to form large abscess cavities. Over them there may be redness and ecchymoses dependent upon how close they approach the surface of the skin. In a week to ten days fluctuation is apparent.

**Pathological Anatomy**—The anatomical changes are those of suppurating processes within the muscles with extensive surrounding round cell infiltration. Not only is the muscle itself involved but also its sheath. The tendons and subcutaneous tissues and skin may also be affected. In other words it is a deep seated disease which may penetrate to the surface or along the muscle planes. It gives all indications of being a pyemia with a special selectivity for the muscular tissue.

**Diagnosis**—At the onset this disease is usually confused with any one of the acute infectious diseases that has an abrupt onset but as soon as the signs of local muscle induration are developed, the real diagnosis is apparent. It is further confirmed by local areas of fluctuation.

**Prognosis**—The muscular abscesses seldom resolve spontaneously and if properly treated healing soon occurs but there is usually a residue of muscular atrophy.

**Treatment**—In the early stages local heat or cold to relieve pain is indicated as well as the general treatment of any acute infection. As soon as fluctuation is detected free surgical drainage should be carried out. If contractures either from malposition or scar tissue eventually develop these should be treated by local passive and active movement and massage and if necessary orthopedic measures.

### Dermatomyositis

**Synonym**—Nonsuppurative myositis

**Definition**—This was at one time principally known by its synonym. It is characterized by a triad of edema, dermatitis and myasthenia.

**Incidence**—It was formerly considered a rare disease in North America and reported chiefly from the Scandinavian countries. In recent years more cases are being recognized here. This is probably due to the fact that the complete clinical pattern is now appreciated as distinct from its several parts.

**Etiology**—The cause is unknown. It is now classed among the group of so called collagen diseases concerning which there is much debate as to etiological factors. Among these a direct or systemic effect of bacterial toxins upon collagen tissues has been advanced while others have suggested an allergic basis. It is most common in middle age next in children but all decades may be affected and equally in both sexes.

**Symptoms**—The onset is occasionally preceded by a history suggestive of transient Raynaud's disease. Otherwise it is insidious with prodromata of weakness, malaise and anorexia. This is soon followed by a rapid appearance of more or less diffuse pains and aches which are soon localized in the muscles rather than the joints and periarticular tissues. One group of muscles after another may be involved until practically the whole musculature has been the site of the lesion. The pain is excruciating and is variously described as boring, tearing or cramplike. There is exquisite tenderness.

The skin lesions are fairly characteristic. In about one third of the cases there is erythema and edema of eyelids and face which is diffuse and of a heliotrope color similar to that found in *Lupus erythematosus disseminata*.

panniculitis, lumbago, muscular rheumatism, etc. Some of these when applied in a strict sense have a reason for their existence, but unfortunately they are used so loosely that they may mean something or nothing. If they are applied in their strict pathological sense, a *fibrositis* would mean a local or general inflammation of the fasciae, muscle sheaths, ligaments, aponeuroses and tendons. Such cases are not unusual. Their general symptomatology is pain 'stiffness of the joints' and muscular weakness. On examination localized tender areas may be found which also give the impression to the palpating finger of local areas of induration.

*Myositis* strictly means an inflammation of the muscles, and *panniculitis* an inflammation of the subcutaneous fatty tissues. Where *fibrositis*, *panniculitis* and *myositis* begin and end or when they are all part of a local lesion is difficult to determine. Painful nodules may be palpated in all of them. They are all aggravated by muscular movement. If not due to a local cause such as trauma they all have a tendency for remissions and exacerbations unless the original cause is removed. Local disturbances of this nature have given rise to a nomenclature which has implied definite diseases and is used as such not only by the laity but also by the profession. In this category may be placed neuralgias, pleurodynia, torticollis, lumbago, indurative or nodular headache, sciatica, etc. It cannot be denied that some of these by their local persistence may in time lead to local anatomical changes and may be most intractable to therapeutic measures, but this does not remove the possibility that in their earliest stages they could have been cured if they had been taken with sufficient seriousness and the local or general cause sought and removed.

There are in addition to these vague signs and symptoms, certain well defined lesions of the muscles and associated tissues of which the following are the most important.

### Primary Suppurative Myositis

**Definition**—This is an acute inflammation of the muscle which may be either single or multiple and has associated signs of acute infection.

**Incidence**—It is a comparatively rare disease in North America and has been most commonly described in Japan and tropical Africa where it goes by the name of *myositis purulenta tropica*.

**Etiology**—It is found in both sexes and at all ages and is usually attributed to an infection by the *Staphylococcus aureus*, the portal of entry of which is not constant.

**Symptoms**—The onset is sudden with a chill and pyrexia. This is also accompanied by the usual general symptoms of infections such as malaise, anorexia, headache, generalized pains and sweating. In a short time localized areas of swelling, tenderness and induration are found in the muscles involved. These may be isolated or occur in groups which may eventually coalesce to form large abscess cavities. Over them there may be redness and ecchymoses dependent upon how close they approach the surface of the skin. In a week to ten days fluctuation is apparent.

groups of muscles involved, while in other cases it may progress to affect all voluntary muscles. There is no sensory change while the electrical reactions in some cases may be reduced and in others lost.

**Pathological Anatomy**—The anatomical changes are first local swellings which are extremely hard. The muscle fibers are eventually replaced by connective tissue, the former undergoing hyaline degeneration. There may be local areas of edema of the skin and connective tissue. The muscles cut with great difficulty, being almost as hard as wood.

**Diagnosis and Treatment**—An exact *diagnosis* rests upon biopsy examination. As already mentioned there may be extensive progression although in time some improvement usually occurs. The *treatment* is purely symptomatic.

### Myositis Ossificans Progressiva

This is a terminal inflammatory lesion of the muscles which eventually become ossified. There is no cause known.

**Symptoms**—The onset of the disease is insidious with vague localized or radiating pains in the limbs. It has been described by Munchmeyer as divisible into three stages. In the first stage there is extensive infiltration both within and between the muscle which leads to the formation and proliferation of connective tissue. It appears to have its origin about the blood vessels. In the second stage the connective tissue becomes much more dense and begins to contract to form hard fibrous masses which include muscle fibers. In the center of these fibrotic areas osteotrabeculae begin to appear which later form osteoblasts and the third stage develops with the ossification of compact and spongy bone. This new bone develops also in the fasciae, ligaments and tendons and resembles normal bone. At times there is edema of the subcutaneous tissues and redness of the skin and pyrexia but this lasts only for a few days. When at rest pain is not a prominent symptom although at night there may be shooting pains in the limbs. The rest of the symptoms and signs are due to the contractures and fixation of the joints by the ossified soft parts. The muscles of the back and neck are first involved and it then spreads to the upper and lower extremities and the face. The hands and feet are the last affected. Exostoses are not uncommon. The changes in the muscles are readily detected by the x ray once calcification has begun. In about 75 per cent of the cases there is a peculiar anomalous deformity of the great toes and thumbs which is due to the retardation of growth of the metatarsal and metacarpal bones with ankylosis.

**Diagnosis**—The diagnosis in the early stages may be difficult but it is usually certain once the deformity of the thumbs and great toes, exostoses and bony deposits in the muscles appear, which can be recognized by the x ray.

**Prognosis**—The prognosis as to life depends upon the degree of the deformity and the rapidity with which complete incapacity develops. There may be difficulty in mastication and respiration due to ossification of the muscles required for these acts. Treatment is of no avail to control the ossification but careful nursing is important to prevent complications and maintain nutrition.

(see page 1411) It has also been described as erysipeloid, roseolar, morbilliform, urticarial, eczematous, and petechial. Almost any combination within these descriptive terms may be found and may affect any part of the skin.

The edema may be localized in the skin lesions or it may be diffuse and simulate scleroderma. In many areas it seems to penetrate deeply through the subcutaneous tissues to the muscles themselves. The edema would appear to be a common attribute of both the skin and muscle lesions.

In addition to the skeletal muscles those of the tongue, pharynx, larynx, esophagus, diaphragm and intercostals may be involved.

Fever is irregularly present and the spleen is often palpable. There is a leucocytosis and in about one fifth of the cases an eosinophilia is present. An excessive creatinuria is the rule. Nephritis is not uncommon.

**Pathology**—Biopsies of the skin when taken early are almost undistinguishable from scleroderma. The skin shows considerable edema and engorgement; the subcutaneous tissues are also edematous with a yellowish serous fluid. The muscles are swollen pale and also edematous and undergo degeneration. The smaller blood vessels are the site of definite "fibrinoid" degeneration with straightening and thickening of the collagen fibers and evidence of friability and smudgy eosinophilic staining. There is also thickening of the smooth muscle of the media, infiltration of the connective tissue fibers, thickening of the intima and finally obliteration with thrombus formation. Cellular infiltration is not conspicuous and occurs in the perivascular connective tissue and in the muscle planes.

**Diagnosis**—The diagnosis is not easy in the early stages but if it be considered many more cases will be recognized and may perhaps be confirmed by biopsy. It is usually confused with erythema nodosum, lupus erythematosus, disseminated scleroderma, rheumatoid arthritis and persistent rheumatic fever.

**Prognosis**—This is serious as over 50 per cent of the patients in the cases collected by Steiner died usually due to involvement of the myocardium or the muscles of respiration or deglutition. In those that survived the edema and skin lesions disappear with atrophy of the skin which becomes boardlike with a brawny texture identical to scleroderma. The muscles atrophy and shrink leading to contractures.

**Treatment**—The treatment is purely symptomatic—rest in bed and analgesics to relieve the intense muscular pain.

### **Myositis Fibrosa** (**Myositis Chronica**)

Myositis fibrosa is an unusual affection of the muscles, of unknown origin. It is characterized by an insidious onset, and successive groups of muscles are gradually involved. It usually first appears in the legs. The most prominent symptom is pain, particularly on movement which eventually forces the patient to bed. The muscles become rigid and contractures usually in the flexor position, eventually develop. It may become arrested with one or more

TABLE XV

SITUATION	BURSA INVOLVED	SYNONYM
Shoulder	Acromion	Hod Carrier's Bursitis
Elbow	Radio Humeral	-----
	Olecranon	Miner's Elbow
Hip	Trochanteric	-----
Knee (superficial)	Prepatellar	Housemaid's Knee
		Nun's Bursitis
	Tibial Tubercle	-----
(deep)	Infra patellar	-----
	Gastrocnemius	-----
	Medial Tibial (Anserine)	-----
	Posterior Tibial (Biceps)	-----
Foot	Posterior Calcaneal	-----
	Anterior Calcaneal	-----
	Anterior Plantar	-----
	Lumbrical	-----

more acute forms this may be considerable while in the chronic types there is usually less secretion and the thickened surfaces may be in apposition

**Treatment**—The treatment in the acute phase is complete rest with fixation of the part and the application of lead and opium fomentations. If the process progresses into a chronic form it may be necessary either to remove the bursa or to destroy it by curettage a gauze pack kept in position to allow the wound to heal completely

## DISEASES OF THE JOINTS

### Introduction

There is probably no group of diseases in which there is so much confusion as those where the symptoms are localized about the joints unless it be diseases of the kidney. This is probably due to the fact that many structures are involved in the constant joint movements of daily activity. Therefore any pain stiffness or discomfort which may be felt is automatically referred to the joints although the articular surfaces may in no way be involved. Furthermore pains in the limbs are of common occurrence not only during the onset of acute infections but also with changes of barometer, after unaccustomed exercise trichiniasis and a host of other diverse conditions. In addition there may be definitely local disturbances which have already been mentioned such as *fibrositis panniculitis fasciculitis neuritis neuralgias myalgias, bursitis* etc. It is seldom that the lesions in arthritis do not involve the periarticular tissues also which may lead to confusion as to what degree of the signs and symptoms are intraarticular and how much is periarticular.

The multiplicity of factors which may cause arthritis makes a simple classification difficult. Some of these have been dealt with in detail elsewhere and therefore will only be mentioned to recall the fact that they form part of this large group. The principal metabolic disturbance is gout which has already been considered (see page 870). Nutritrophic conditions are represented by the Charcot's joints of locomotor ataxia and syringomyelia and to a less definite degree by intermittent hydrarthrosis. In all hemorrhagic con-

Localized or traumatic ossifying myositis may follow a severe muscle injury. It remains localized and if the underlying bone has also been injured, the bone, muscle and fibrous tissue may be consolidated into one bony mass.

### Myalgia

In the introduction to this section reference was made to the vague and sometimes acute local muscular pains with muscle spasm. This is a comparatively common condition and chiefly is found in the muscles of the lumbar region (lumbago), in the trapezius (trapezius myositis), and in the cleido sternomastoid (torticollis). Many agents have been ascribed as causing these conditions. They are sometimes most intractable to treatment, but principally they are of importance in the differential diagnosis of other conditions which may give pain in these particular regions, especially as this so in the first two. It is difficult to classify them as separate diseases although localized induration may sometimes be detected on palpation. If after a most thorough search no general or local cause can be found for the pain and rigidity of the muscles the condition is best treated by analgesics and salicylates and local applications of heat, massage, and acupuncture.

### Bursitis

There are placed in different parts of the body, structures called bursae which are serous lined compartments situated where there is friction by the movement of soft parts over firmer and more deeply placed structures. The topography of many of these is well known, but connective tissue has the capacity of producing new bursae if they are required on account of oft repeated but unusual types of movement in the limbs. Therefore they may be found in situations which are not considered to possess them.

**Symptoms and Signs**—The symptoms and signs of bursitis are usually constant and are only modified by their situation. The principal one is pain on movement of the part due to the rubbing together of the inflamed and roughened serous surfaces. There is also local tenderness and frequently swelling due to a serous exudate into the sacs which at times may be acutely inflammatory with round cell and leucocytic infiltration and exudate. The pain is relieved when the surfaces are separated by exudate unless there is surrounding inflammation.

The bursae are most numerous about the knee where Virchow found seventy, although they were not all constantly present. It would not serve a useful purpose to describe the clinical features of all in detail. The bursae principally affected are given in Table XV.

**Pathological Anatomy**—The anatomical changes in bursitis are common to all sites. The endothelial cells may fail to secrete the viscous serous fluid which prevents friction and for which purpose the bursae are formed. The lining may be thickened and changed from a single layer of flat cells to several layers, and they may become cuboidal or columnar in shape. The degree of acute inflammatory reaction varies considerably from case to case. In the



meningococcus, tuberculosis, brucellosis, dysentery, influenza, *Ordium coccidioides*, glanders, smallpox, measles, and diphtheria.

**Symptoms**—The symptoms vary with the severity of the local lesion. Pain is present but varies considerably, not only in different joints of the same case but in different cases. The vague pains of spondylitis and hip joint disease are often mistaken for neuritis, sciatica, myositis, fibrositis, etc. The pain due to arthritis is aggravated by movement and has associated with it muscular spasm, atrophy, and frequently deformity. In the more superficial joints such as the shoulder, elbow, wrist, knee, and ankle, and the smaller joints of the hands and feet, local swelling, tenderness, redness, and limitation of movement are conspicuous signs. If the arthritis develops during the course or convalescence of one of the diseases mentioned above, there is little doubt as to the etiology. In addition to the local signs, there may be pyrexia, chills, and sweats, particularly if there is a purulent process within the joint.

**Pathological Anatomy**—The anatomical changes vary considerably from a mild inflammatory reaction to considerable destruction, not only of the synovial membrane and cartilages but also of the periarticular tissues, and perforation of the joint with sinus formation may occur. The inflammatory reaction is similar to that which would occur with the specific organism in other tissues.

**Diagnosis**—The diagnosis depends upon the appreciation of the possibility of a secondary or metastatic arthritis occurring in the course of a specific acute infection. The mistakes of omission are most frequent when the spine or hip joints are involved, and as has been intimated above, the arthritis may be mistaken for milder and less serious causes of local pain. The true diagnosis is usually arrived at by a careful history, the local symptomatology, and x-ray examination. The more indolent forms such as those due to tuberculosis, syphilis, and typhoid fever often give more difficulty.

**Prognosis**—The prognosis depends upon the infecting organism. The most serious are lesions due to meningococcus, staphylococcus, streptococcus, and the *Ordium coccidioides*.

**Treatment**—The treatment is in the first instance that of the general disease which has caused the arthritis. The local treatment consists of rest, heat or cold, and such specific therapy as may be indicated. It is well to immobilize the joint or joints either in splints or in plaster of Paris shells to prevent contractures and other disabling postural effects. If a purulent exudate or excessive aspiration of the joint cavity is indicated, and when there is evidence of local destruction, surgical interference with free drainage may be imperative. Each case and joint must be dealt with on its own merits.

### Chronic Nonsuppurative Arthritis

We have now to consider a group of cases of arthritis which are in a state of considerable confusion. There are numerous classifications and synonyms are used by different authors to mean different things. Some of these are the following: rheumatoid arthritis, arthritis deformans, osteoarthritis, hypertrophic arthritis, degenerative arthritis, senile rheumatism, chronic rheumatism, atrophic arthritis, infectious arthritis, etc. The confu-

ditions extravasations into the joints may occur, and these are principally represented by hemophilia and scurvy. In fact, in the former disease limitation of movement of one or more joints subsequent to slight trauma may be an outstanding feature. Trauma may also produce a local arthritis and where there is dislocation of the semilunar cartilages of the knee joint recurrent pain and effusion into the joint may lead to considerable impairment of function. There are also cases which can be attributed to occupational or postural strain. Primary or metastatic tumors may invade the joint, producing local arthritic lesions. Disturbed joint function can also be attributed to contractures resulting from local nerve injuries, or the results of poliomyelitis or hemiplegia. Arthritis is often associated with serum sickness, and occurs in those sensitive to foods or other allergens. In all of these conditions there is either a local or systemic cause which can be detected as a rule. There are, in addition, certain local disturbances of the bone in apposition to a joint which may lead to disability. Among these may be mentioned osteochondritis, Perthes' disease, and Koehler's disease, descriptions of which will be found in textbooks on orthopedics or surgery.

There now remain to be considered three groups of arthritis, namely, the septic arthritis, chronic nonsuppurative arthritis, and osteoarthritis.

### Septic Arthritis

Septic arthritis is frequently called infective arthritis which however, is a designation which leads to confusion. In all these cases a microorganism is present in the joint cavity. It may be carried there by the blood stream, or a septic focus in the neighboring bone may rupture into the joint, or it may be induced through a penetrating wound. The second and third causes do not particularly interest us at the moment as they are purely local lesions and are obvious both as to etiology and treatment.

Septic arthritis due to the transportation of microorganisms by the blood stream is always secondary or metastatic to some systemic infection. It is principally caused by the streptococcus as in cases of streptococcal septicemia, erysipelas and scarlet fever. In the last disease there may be an arthritis which is difficult to distinguish from rheumatic fever. This has already been dealt with. In other cases there is a frank suppurative process occurring in one or more joints. In these cases cardiac involvement does not occur. The other organisms which play a part in producing septic arthritis include the staphylococcus, gonococcus, pneumococcus, treponema pallidum and typhoid bacillus. The arthritis due to such organisms is usually an exudative process but during convalescence from typhoid fever the so called typhoid spine or hip may develop. There has been considerable discussion as to whether typhoid spine is a neurosis or is caused by definite anatomical changes. The same may be said of the similar affection of the hip. In some instances a chronic osteitis of the hip and neck of the femur has been found and also occasionally x ray evidence of a spondylitis has been detected. The majority of the cases, however do not show organic changes. Specific infectious diseases which may less frequently cause arthritis as a secondary lesion are

meningococcus, tuberculosis, brucellosis, dysentery, influenza, *Oridium coccidioides*, glanders, smallpox, measles, and diphtheria.

**Symptoms**—The symptoms vary with the severity of the local lesion. Pain is present but varies considerably, not only in different joints of the same case but in different cases. The vague pains of spondylitis and hip joint disease are often mistaken for neuritis, sciatica, myositis, fibrositis, etc. The pain due to arthritis is aggravated by movement and has associated with it muscular spasm, atrophy, and frequently deformity. In the more superficial joints such as the shoulder, elbow, wrist, knee and ankle, and the smaller joints of the hands and feet, local swelling, tenderness, redness and limitation of movement are conspicuous signs. If the arthritis develops during the course or convalescence of one of the diseases mentioned above, there is little doubt as to the etiology. In addition to the local signs there may be pyrexia, chills and sweats, particularly if there is a purulent process within the joint.

**Pathological Anatomy**—The anatomical changes vary considerably from a mild inflammatory reaction to considerable destruction, not only of the synovial membrane and cartilages but also of the periarticular tissues, and perforation of the joint with sinus formation may occur. The inflammatory reaction is similar to that which would occur with the specific organism in other tissues.

**Diagnosis**—The diagnosis depends upon the appreciation of the possibility of a secondary or metastatic arthritis occurring in the course of a specific acute infection. The mistakes of omission are most frequent when the spine or hip joints are involved and as has been intimated above, the arthritis may be mistaken for milder and less serious causes of local pain. The true diagnosis is usually arrived at by a careful history, the local symptomatology and x-ray examination. The more indolent forms such as those due to tuberculosis, syphilis, and typhoid fever, often give more difficulty.

**Prognosis**—The prognosis depends upon the infecting organism. The most serious are lesions due to meningococcus, staphylococcus, streptococcus and the *Oridium coccidioides*.

**Treatment**—The treatment is in the first instance that of the general disease which has caused the arthritis. The local treatment consists of rest, heat or cold and such specific therapy as may be indicated. It is well to immobilize the joint or joints either in splints or in plaster of Paris shells to prevent contractures and other disabling postural effects. If a purulent exudate is excessive, aspiration of the joint cavity is indicated and when there is evidence of local destruction, surgical interference with free drainage may be imperative. Each case and joint must be dealt with on its own merits.

### Chronic Nonsuppurative Arthritis

We have now to consider a group of cases of arthritis which are in a state of considerable confusion. There are numerous classifications and synonyms are used by different authors to mean different things. Some of these are the following: rheumatoid arthritis, arthritis deformans, osteoarthritis, hypertrophic arthritis, degenerative arthritis, senile rheumatism, chronic rheumatism, atrophic arthritis, infectious arthritis, etc. The confu-

sion will be more confounded if a rigid classification is constructed upon definite anatomical changes, as these are not always constant throughout the whole course of the disease. When the different synonyms are sorted out there will be found two main varieties of arthritis, as follows: rheumatoid arthritis, arthritis deformans, atrophic arthritis, proliferative arthritis, all being applied to more or less the same symptom complex, and the second group will comprise osteoarthritis, hypertrophic arthritis, degenerative arthritis, and such local arthritic diseases as morbus coxae senilis, and Heberden's nodes. In the present description the terms "rheumatoid arthritis" will be used to signify the first group and "osteoarthritis" the second.

### Rheumatoid Arthritis

**Etiology**—The etiology of this disease—if it be a specific disease—is not known. The causes which have been considered as playing a part in its production may be divided into the predisposing and the exciting. Among the former have been included physical and emotional shock, trauma, exposure to cold and dampness, fatigue, constitutional characters, heredity, climate etc. Most of these have been accused of being predisposing factors in many chronic diseases. It is common in the history of a case of rheumatoid arthritis to find a record of other members of the present or past generations having suffered from a similar disease. It is a disease of the temperate zones, being rarely found in the Tropics. The first manifestations usually appear before the thirty-fifth year. It is not unusual to encounter severe cases with considerable deformity and rapid muscular wasting in young unmarried women. These have been considered by some to be connected with the sexual cycle. The author has known married women who were only free of symptoms when pregnant but after the thirteenth and fourteenth child this prophylaxis seemed to have been limited to a reasonable limit. Jaundice has been reported as having a similar effect.

The exciting causes of this disease continue to be a matter of controversy which revolves around the decision as to whether it be an infectious disease or not. The principal evidence marshalled in favor of its being so is the supposed frequency of focal infections about the teeth, in the tonsils, paranasal sinuses, gallbladder, prostate, colon, cervix uteri, and pelvic adnexa. It is quite true that such an infection may be found in a person with rheumatoid arthritis but on the contrary, they are also found in as many, if not more that do not have this disease. It is still far from proved that focal infections are directly responsible for this disease. Another school of thought has been in favor of the disease being an allergic phenomenon. Considerable fragmentary evidence can be marshalled in favor of both theories. Particularly in favor of the first has been the finding by Cecil, Nicholls, and Stansby, of an attenuated streptococcus in the focal infections, a similar streptococcus being recoverable from the blood and joints in a goodly percentage of patients, a higher agglutinin titer for the *Streptococcus hemolyticus* in their blood as compared to controls, high precipitation of the streptococcus protein and carbohydrate with the serum of these patients, and finally the production of a chronic progressive

arthritis by repeated streptococcus injections in rabbits which closely resembles rheumatoid arthritis in man. The first and last of these points have not been by any means unanimously accepted, and the second and third have been claimed to indicate an allergic condition. Other conditions which have been suggested

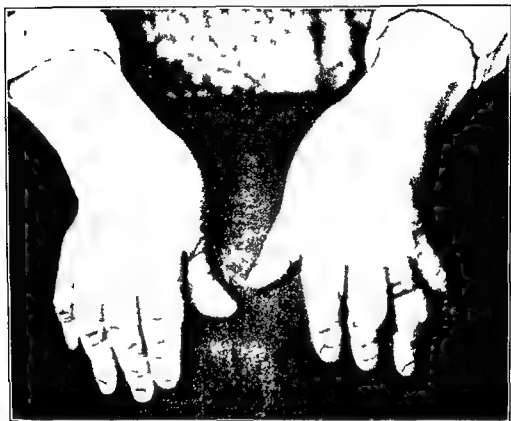


Fig 448—Photograph of the hand in a case of rheumatoid arthritis in the acute stage showing swelling of the wrists and fusiform enlargement of the fingers



Fig 449—Photograph of the hand in a case of arthritis deformans showing atrophy, fusiform swelling of the fingers and ulnar deformity

as being exciting factors in this disease are various anatomical changes in the gastrointestinal tract particularly a redundant and hypotonic colon and finally more recently Rinehart has shown experimentally an important rela-

tionship between the joint lesions of scurvy, rheumatic fever\* and rheumatoid arthritis, and those produced in animals by a deficiency of vitamin C. It would be unwise to be dogmatic as to the cause of this disease at the present juncture. There is something to be said in favor of any of these causes being operative, but none of them are beyond reproach, and all are open to considerable criticism.

Recently it has been suggested that rheumatoid arthritis should be grouped with the so called "collagen diseases." This has been based on the widespread finding of fibrinoid degeneration of the collagen or fibrous connective tissues. This does not carry the question of etiology to a more definite conclusion but it does emphasize the concept that this is a systemic disease and that the arthritic manifestations are only one evidence of a widespread process.

**Symptoms**—The onset of rheumatoid arthritis may be either acute or insidious. In about 50 per cent of the cases it can be definitely dated, and is often accompanied by low grade pyrexia, headache, general malaise, and frequently splenomegaly and lymph adenopathy. The joint symptoms in the beginning may be migratory. The first to be involved are usually the knees and fingers, followed by the shoulders, wrists, ankles, elbows, until ultimately practically every joint in the body can be affected.

When the onset is insidious one joint only may be affected, and remain so with varying intensity for weeks or months. Gradually other joints follow until eventually both the acute and the insidious reach the same stage.

The local disturbances are a variable degree of pain which is not always in proportion to the swelling. This latter is best seen in the fingers which have a fusiform or sausage like shape. In time contractures lead to considerable deformity in these parts. There is often flexion of the proximal phalanges and hyperextension of the terminal ones, while other joints show lateral deviation and subluxation which combine to produce quite bizarre deformities (see Fig. 449). The larger joints are similarly affected and exhibit swelling, local redness, increased local temperature, tenderness, and effusion.

The constitutional symptoms are important. Secondary anemia and considerable emaciation are the rule in well established cases. Good nutrition and no anemia is the exception. Apart from the local heat about the joints, the limbs are usually cold and clammy and there is lowering of the surface temperature probably due to vasoconstriction of the capillaries which are conspicuously restricted both in numbers and size. There is also a lowered sugar tolerance and the sedimentation rate is rapid. All these systemic reactions point to a general disturbance of the physiological control.

It must be appreciated that all cases of this disease do not present the classical features as here described. There are many variants in the extent and severity of the arthritic changes and systemic reactions. It may be taken as a general rule that the younger the victim the more violent is the disease. It is the irregular case that gives the most trouble in assessing the true nature of the disease.

It might be considered advisable to deal with rheumatic fever amongst diseases of the joints but, the author does not consider this proper as the arthritis in this disease is merely an incident. In spite of the fact that fibroid nodules develop in both diseases and occasionally cardiac lesions occur in cases which are supposed to be arthritis deformans.

There are several forms of this disease which warrant special mention. The first is a spondylitis which is described as the 'Marie Strumpell' type. It is characterized by the so called 'poker spine' caused by the vertebrae being bound together into a solid mass by fibrous tissue (see Fig 450). It is interesting to note that the lesion begins in the vertebral joints where a pannus



Fig 450—X ray of the spine showing the spondylitis of the Marie Strumpell type

destroys the intervertebral discs in a manner similar to that in classical arthritis deformans. But in distinction to this form the smaller joints of the hands, feet, fingers and toes are seldom involved, nor is there the wasting of the muscles of the hands, feet, legs and forearms. The vascular and thermal changes of the skin, etc., also are not found. On the contrary, the larger joints, particularly the hips and shoulders, are likely to be affected either in sequence or independ-

ently. It is most important to appreciate that in classical rheumatoid arthritis the progress of the joint involvement is usually centripetal, while in the 'Marie Strumpell' form it is centrifugal.

The second type requiring special mention is an acute to chronic arthritis in children, "Juvenile arthritis deformans," or 'Still's disease' (see Fig 451). In addition to the joint lesions which are similar to those of rheumatoid arthritis there is a lymphadenopathy, splenomegaly and hepatomegaly and myeloid degeneration of the viscera has been reported. Telford, in 1924, described a group



Fig 451—Photograph of a child with juvenile arthritis deformans or Still's disease

of cases in adults which were characterized by arthritis, splenomegaly and leukopenia. He considered it a specific syndrome and it became known by his name. It is now not considered to be a separate disease but an atypical form of rheumatoid arthritis related except for the age period to 'Still's disease'.

The x-ray findings in rheumatoid arthritis and 'Still's disease' chiefly consist in a narrowing of the articular spaces, a rarefaction of the bones and finally a complete destruction and fusion of the articulating surfaces showing no lifting or spurting, but the fusion may be a bony ankylosis with extension of the bone marrow from one bone to another. The loss of contour and the



fusion of the bones is best seen in the wrists and fingers. The contractures produce subluxations which can be detected by palpation and by the x ray which often reveal the articulating surface of one bone impinging upon the shaft of its neighbor.

Small punched out areas are often seen in the smaller bones. This may closely resemble the x ray lesion seen in gout and Boeck's sarcoid. Indeed, the differential x ray diagnosis may be extremely difficult.

**Pathological Anatomy**—The first and most characteristic anatomical finding is the development of a pannus within the joint due to proliferation of a synovial membrane. This is eventually converted into granulation tissue which spreads over the whole cartilage producing extensive destruction of it.

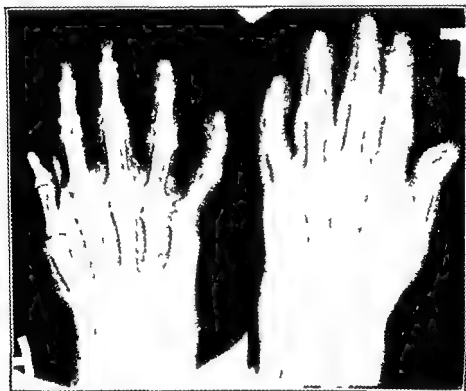


Fig. 45.—X ray of the hand in a case of arthritis deformans showing decalcification, narrowed joint spaces and soft tissue swelling.

This proliferative process finally involves the capsule and periarticular structures. It is a true inflammatory process and in time leads to complete destruction and obliteration of the articular cavities. Fibroid nodules similar to those encountered in acute rheumatic fever are sometimes found.

There was referred to above under Etiology the systemic finding of a diffuse fibroid degeneration of the collagen tissues. This is widely distributed through many structures wherever these tissues may be found. It therefore raises the concept of rheumatoid arthritis including most of its variants from that of a local lesion to the status of a systemic disease in which the

joint lesions are but a visible manifestation. Without this appreciation of the general character of the disease, the approach to its proper handling is unrealistic.

**Diagnosis**—In a well established case the diagnosis is seldom in doubt. The more important points to differentiate it from other joint lesions are its occurrence in young adults, the migratory character of the arthritis, the characteristic form of the fingers and the presence of a general systemic reaction indicated particularly by pyrexia, emaciation, muscular atrophy, lowered surface temperature of the extremities, and local sweating. The arthritis itself may be confused with subacute and chronic septic arthritis, particularly the gonorrheal form, subacute and chronic rheumatic fever, gout, and osteoarthritis.



Fig. 453.—X ray of the hands in a case of rheumatoid arthritis in a more advanced state than seen in Fig. 45, showing destruction of the carpal bones and decalcification.

Its differentiation from gonorrheal arthritis is based upon the presence of a specific pelvic or prostatic infection, although this is not absolutely necessary as the signs of infection at the portal of entry may have disappeared and still an active arthritis may be present. It can be further differentiated by the fact that gonorrheal arthritis usually localizes in one or more of the larger joints. The diagnosis may be aided by the presence of a positive gonorrheal fixation test. Subacute and chronic rheumatic fever can give rise to considerable difficulty in diagnosis. It must be remembered that this infection varies in the intensity of its local manifestations at different age periods. In childhood the cardiac and nervous symptoms dominate the picture, but if

the first attack occurs after thirty these symptoms may be comparatively insignificant and the main features are arthritic signs — low grade persisting pyrexia, a slight leucocytosis and sweats. There is also an increased sedimentation rate and in these cases fibroid nodules of a gross character are not unusual. Of considerable importance in these cases is the detection of a prolongation of the P-R interval in the electrocardiogram. It may take some



Fig 454—Fibroid nodule about the elbow in a case of chronic arthritis. Note also the deformity of the fingers.

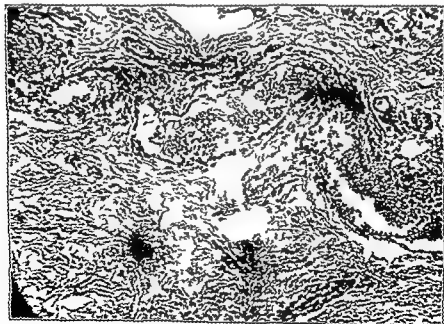


Fig 4 —Photomicrograph of a fibroid nodule shown in Fig 454

time before a differentiation of diagnosis can be arrived at. The prognosis in the two conditions is quite different, being more favorable in the chronic rheumatic fever at this age.

The incidence of gout in North America has not received the attention which it should in recent generations. It is more likely that a case of gout would be confused with rheumatoid arthritis than the contrary. The characteristic x-ray findings and the high uric acid in the blood should readily clarify the diagnosis if gout is considered as a possibility. The differential diagnosis of rheumatoid arthritis and osteoarthritis often presents considerable difficulty. There are certain points, however, to be constantly borne in mind. Osteoarthritis seldom occurs before the fifth decade. The patient is usually overweight. The joints principally involved are the knees, spine and hip, and the arthritis remains localized and is in no way migratory. There is no periarticular swelling except that Heberden's nodes are practically always present. The x-rays show bonyipping of the margins of the joints. There is seldom any deformity or ankylosis. The serological and blood examinations are negative. All these features are the opposite to what is found in rheumatoid arthritis. There is, however, no reason to be dogmatic that either one of these lesions is present alone, as it is not unusual for signs of osteoarthritis to develop in later years in a case of rheumatoid arthritis.

The varying quality of the joint lesions in rheumatoid arthritis is often a source of much confusion. To substantiate the diagnosis there must also be present evidence of a systemic disorder, such as unwarranted fatigue, accelerated sedimentation rate, atrophy of the skeletal muscles, weight loss and general debility. Psychic factors are at present difficult to assess, but their presence constitutes an important phase in this disease which the future must unravel.

**Prognosis**—The prognosis as to life is good but the progress of the disease to a disabling state is always problematical. Many cases do not proceed beyond the initial stages, while in others it is a steady, progressive disability. The presence of an increased sedimentation rate, and of specific streptococcal agglutinins are indicative of continued activity, while their approximation to normal is indicative of improvement.

**Treatment**—The treatments in the past for rheumatoid arthritis have been almost innumerable and as would be expected most of them have been entirely useless. An important development of the recent investigations and study of this disease has been to place the therapy on a more rational basis. If it be a chronic infection or the result of a chronic infection it would seem reasonable that it should be treated along the same lines as tuberculosis. Therefore such a plan of action should be instituted early in the disease. In fact the time is long overdue when this problem should be attacked in the same manner as tuberculosis and institutions for its rational treatment be established such as were advocated for acute rheumatic fever (see page 67). General bodily rest and the avoidance of fatigue are of prime importance, as is also an adequate diet rich in vitamins. There are those who consider certain restrictions of diet of importance, particularly the limitation of carbo-

hydrates but as rheumatoid arthritis is usually underweight and anemic dietary restrictions must be carried out with great caution as they may defeat the general plan of supportive treatment. A high vitamin diet is best attained by giving cod liver oil, yeast and fruit juices in maximum amounts.

The removal of focal infections was enthusiastically followed some years ago. In fact the removal of these seemed to assume a greater prominence than the treatment of the patient and the arthritis. As in all chronic diseases the patient must be placed in the best possible state of general health, and part of this is the removal or correction of focal infections; in fact this applies to those in good health as well as to invalids. On the other hand ruthless removal of suspected teeth, tonsils, gallbladders and appendices can be carried out to a harmful degree and furthermore the time should be carefully chosen for such procedures. They should not be undertaken when the arthritis is in a period of acute exacerbation and if extensive removal of focal infections is required this should be done in stages rather than to subject the patient to an exhausting ordeal.

Specific and nonspecific protein therapy have had their periods of popularity. The principal substances used in nonspecific foreign therapy have been typhoid vaccines, milk and milk products. Much of the former enthusiasm has now been replaced by a more rational scepticism. It is true that in active stages temporary improvement may be expected. The severe and sometimes dangerous reactions and other unpleasant features from the patient's point of view hardly justify their use. Specific foreign protein therapy in the form of vaccines rests on a more rational basis. The principal vaccines employed have been prepared with hemolytic streptococci and at one time these were given intravenously with—as would be expected—frequent severe general reactions which simulated the reactions of nonspecific protein therapy. If vaccines are to be used it is most important that general reactions should be avoided as otherwise although they may be followed by a temporary improvement in many they aggravate the condition or may precipitate an exacerbation. This is also true of all foreign protein reactions. The subcutaneous administration of streptococcal vaccines should be adhered to if they are to be given at all and should follow the general principles of tuberculin therapy, that is the initial doses should be minimal. It is best to start with a dosage of about ten million streptococci and gradually increase by one half this number every four days. It is better to be cautious than to run the risk of producing general reactions. The vaccine should be continued for many months or until it is certain that the patient has developed a definite resistance to it. If no improvement is then apparent it should be discontinued. The invasion by clinicians of the realm of immunology of the principles of which they are pathetically ignorant is no credit to the science or even the art of medicine.

In addition to the general bodily rest and rational life the affected joints themselves should not be neglected. They should be placed by means of plaster of Paris shells in a position which will relieve all strain upon the joints. These should be worn particularly at night. During the daytime regular courses of passive movements and in time active exercises should be

instituted, but as long as the joints are in an acute stage, activity should be avoided. Such treatment requires meticulous attention upon the part of the knowledgeable physician, and if success is to be attained, absolute discipline should be required of the patient. On the other hand, immobility to the extent that the joints become "frozen" should be avoided. There is a happy mean between the ankylosis of disuse and too early active movements. A hazard which is too often neglected is that of phlebothrombosis with the risk of pulmonary embolism which may result from prolonged immobility of a limb. This can be avoided by posture and frequent simple massage to assist venous return in the affected part.

*Physiotherapy*, both local and general, has had its enthusiastic supporters. It should be used by all means but with a reasonable appreciation of what it may attain. There are numerous spas where various forms of this therapy are carried out. It is done in these institutions under strict supervision, and there is no doubt that considerable improvement, although sometimes unfortunately of a temporary character, is often obtained. The use of heat, both locally and in producing artificial pyrexia, has been much employed of late. The former may be accomplished by hot baths, electric light baths or the immersion of joints in solid paraffin with a low melting point. All of these measures may produce local hyperemia and comfort. Artificial pyrexia induced by diathermy and other measures would appear to simulate the effects expected from foreign protein therapy and so far the results have been on a par with this, although the reactions are under better control.

*Drug Therapy*—Many drugs have been employed in the treatment of this disease but no conspicuous success has resulted. Any apparent improvement results from the relief of pain and therefore the most popular are the salicylates and allied compounds. These may be given in the form of aspirin to the amount of 40 grains a day but should not be used to the neglect of other therapy. Gold therapy has its enthusiastic advocates. There is no evidence to indicate that it is a specific and its use is frankly empirical. However from reported cases about 60 per cent of cases seem to be improved by its use but of these about 50 per cent have a relapse either following or during treatment. This therapy should be started cautiously with gradually increasing amounts but the maximum should not be more than 50 mg of the gold salt (50 to 60 per cent gold) once a week. Regular checks of the hemoglobin, leucocytes and nonprotein nitrogen should be carried out. The continuation of a maintenance dose of 25 mg every fortnight is recommended. Anemia should be combated with iron while periodic blood transfusions are of great benefit. The use of highly concentrated vitamin D in enormous doses has also a present vogue. There is here a real danger unless the therapy can be controlled by frequent blood calcium determinations and the dietary calcium strictly supervised (see page 806). The author has seen three deaths from hypervitaminosis in this treatment (see Figs. 316 and 317).

The lowered surface temperature and sweating, particularly of the limbs with the persistent pain led Rowntree and Adson to employ sympathetic ganglionectomy and ramisectomy in the hope of producing changes in the

vasomotor control of the extremities and so increase the local blood supply. This was rewarded with gratifying results in certain of the more chronic and refractory cases. Operations for the reduction of contractures and subluxation may at times be required in chronic and neglected cases.

### Reiter's Disease

Reiter in 1916 described a syndrome characterized by purulent urethritis, chronic polyarthritis and conjunctivitis. He claimed it was caused by a spirochete and called it *spirochetosis arthritica*.

The onset is usually with a urethritis which is not venereal in origin and the causative agent has not been determined. The spirochetal origin is not accepted.

Although the triad mentioned above is usually present this is not necessarily the case. In addition skin lesions sometimes occur in the form of a keratoderma and Larran has reported prolongation of the auriculoventricular conduction. This diffuse distribution of lesions would suggest a systemic dissemination of the causative agent.

The course of the disease tends to be chronic with remissions and exacerbations. The eventual outlook is good as to life but occasionally keratitis and iritis may lead to permanent ocular injury while the joints rarely are disabled.

There is no known treatment; chemotherapy and antibiotics are useless.

### Palindromic Rheumatism

In 1944 Hinch and Rosenbergs reported a recurring form of arthritis which they called palindromic rheumatism. This was characterized by a recurring nonsuppurative arthritis without febrile or other systemic manifestations. The onset was sudden with pain, swelling, redness and impaired function of one or many joints. The reaction would indicate involvement of both the arthritic and periarthritic tissues. It would last for a few hours to several days, as rapidly disappear and recur at shorter or longer periods over many years. There was no permanent joint disability but it cannot be said that the condition was ever cured. The cause has never been ascertained but the whole course and local character of the lesion strongly suggests an allergic reaction. The treatment is symptomatic to relieve pain. Morphine and allied drugs should never be prescribed although they may be given occasionally by the physician.

### Osteoarthritis

The application of the term arthritis to this condition is hardly justifiable as it is really an arthropathy.

**Etiology**—The cause is not known but there are a number of factors which might seem to enter into its production. It is a degenerative lesion and runs closely parallel with other conditions which are influenced by age. The patients are usually overweight and the joints principally affected are those which would be subject to static or other trauma such as the spine, hips,

knees and fingers It is also found frequently in those engaged in heavy occupations Perhaps the most important single factor is a familial pre disposition

**Symptoms**—The onset is insidious and the condition is often recognized accidentally in x rays taken for other purposes The symptoms are few and develop when the exostoses or eburnations affect the movement of the joints There are seldom any local signs unless the exostoses reach such a magnitude as to be palpable, although crepitation may be felt and heard but is usually painless The x ray picture reveals bony lipping and spurs along the margins of



Fig 4 6—X ray showing morbus coxae senilis of both hips

the articulations In advanced cases there may be rarefaction in the metaphysis and a narrowing of the joint space and changes in shape, although the articular surface remains well defined The most common form of this disease is the so called *Heberden's nodes* which appear in middle life in the terminal phalanges and are most common in women It is seldom that they are painful or interfere with movement although occasionally this may be the case

There now is considered to be an association between this osteoarthritis and lesions of the cartilaginous structures of the joints A good example is the occurrence of spurs or exostoses at the vertebral margins in cases of herniation of the *nucleus pulposus* The same may be found in the cir



ligamentous components of the knees, hips, and occasionally the shoulder, ankle and elbow. In *Martin's disease* (see p. 456) is an example the principal feature is a destruction of the joint cartilages both of the acetabulum and the femur and eburnation around the periphery of the former. In the spinal lesions these may be difficult to detect before pronounced symptoms and signs indicative of pressure upon the spinal roots have developed. The diagnosis and therapy of these spinal lesions have now become an important department

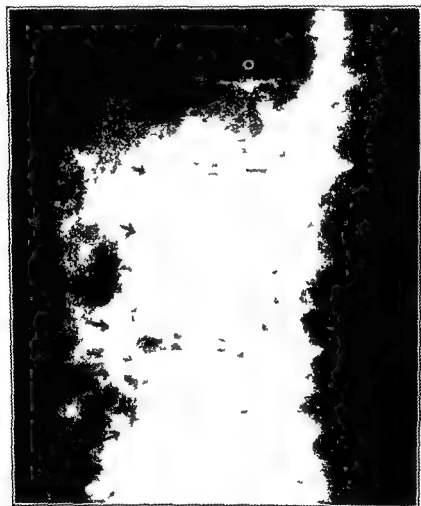


Fig. 45.—Lateral x-ray of hip joint in a case of ankylosing arthritis. Note the bony outgrowth indicated by the arrows.

to both the orthopedist and neurosurgeon but should always be within the concept of the internist as a cause of back pain and peripheral root symptoms and signs.

The principal feature in this form of arthropathy is pain which may radiate along the distribution of the spinal roots and nerves as for instance in lesions of the hip the pain may radiate down the thigh and lead to suspicion of a lesion of the knee joint. Those of the spine may be called sciatica low

knees and fingers. It is also  
occupations. Perhaps the most  
disposition.

**Symptoms**—The onset is insidious  
accidentally in x rays taken for other  
develop when the exostoses or eburnation  
There are seldom any local signs unless  
to be palpable, although crepitation may be  
less. The x ray picture reveals bony lipps



Fig. 456—X ray showing morbus coxae / arthritis of both hips

the articulations. In advanced cases there may be rarefaction in the metaphysis and a narrowing of the joint space and changes in shape, although the articular surface remains well defined. The most common form of this disease is the so called *Heberden's nodes* which appear in middle life in the terminal phalanges and are most common in women. It is seldom that they are painful or interfere with movement although occasionally this may be the case.

There now is considered to be an association between this osteoarthropathy and lesions of the cartilaginous structures of the joints. A good example is the occurrence of spurs or exostoses at the vertebral margins in cases of herniation of the *nucleus pulposus*. The same may be found in the ear

ligamentous components of the knees, hips, and occasionally the shoulder, ankle and elbow. In *Martin's coxae scindis* (see Pl. 46) as an example the principal feature is a destruction of the joint cartilages both of the acetabulum and the femur and charnation around the periphery of the former. In the spinal lesions these may be difficult to detect before pronounced symptoms and signs indicative of pressure upon the spinal roots have developed. The diagnosis and therapy of these spinal lesions have now become an important department



Fig. 45.—Lateral x-ray of the lumbar spine in a case of osteoarthritis. Note the bony outgrowth indicated by the arrows.

to both the orthopedist and neurosurgeon but should always be within the concept of the internist as a cause of back pain and peripheral root symptoms and signs.

The principal feature in this form of arthropathy is pain which may radiate along the distribution of the spinal roots and nerves. As for instance in lesions of the hip the pain may radiate down the thigh and lead to suspicion of a lesion of the knee joint. Those of the spine may be called sciatica low

back pain, lumbago, or other indefinite syndromes. This signifies the importance of a detailed examination by x ray and other means to reach a factual diagnosis upon which will rest a rational therapy.

There is a group of cases of osteoarthritis which are thought to be associated with the menopause. There is little evidence to suggest that this is more than a coincidence, as osteoarthritis usually appears earlier in women than in men, and as at this time there is often a rapid increase in weight, and as the fifth decade is the period when the lesion is most commonly manifest, it is not at all surprising that this correlation suggests itself. The knees are most affected and many of these women have a faulty posture (high heels and bad shoes) and flat feet are common. The vertebrae and feet are also frequently involved, but other joints may be affected. The symptoms are those already described for osteoarthritis, and the x ray appearances are identical. The course of the disease is insidious and continuous, and although it may be arrested, regression never occurs.

*Senile or senescent arthritis* is merely a form of osteoarthritis. It is principally found in the spine, fingers, and the larger joints of the arms and legs. It is indistinguishable from other forms of osteoarthritis except that it develops in the later decades.

Osteoarthritis of the spine, or *hypertrophic spondylitis*, as it is sometimes called, is also a form of the same disease in which the principal bony changes are found in the vertebrae. It may give rise to considerable limitation of movement. It is otherwise symptomless unless the exostoses produce nerve pressure. The pain in these conditions has a spinal distribution. Very severe and agonizing pain may suddenly occur if through a sudden violent effort one of these exostoses is broken loose. It is surprising at times what a slight degree of muscular exertion may produce this. Other joints are usually also involved, especially the hips and knees.

**Anatomical Changes**—The anatomical changes in osteoarthritis are purely degenerative, there being a progressive absorption and production of bone which leads to the distorted and irregular ossification about the joints. This is produced and aggravated by trauma either direct or from faulty posture. The joint cavity itself is practically never involved.

**Course**—The course is extremely insidious and although true ankylosis does not occur locking of the joint may result from impingement of the exostoses.

**Treatment**—The treatment is principally confined to the protection of the involved joints. This protection consists of the avoidance of trauma and also in exercises which will improve the faulty posture. A reduction in weight in those who are obese is important to accomplish these ends and therefore the patient should be placed on a subcaloric diet. Thyroid extract, potassium iodide, high vitamin diet and numerous other therapeutic procedures have been advocated, but their effects are to say the least doubtful. Pain in the affected joints is often relieved by physiotherapy and particularly local heat. Massage and passive movements are to be used cautiously to avoid producing additional local trauma. The role of infections was at one time overempha-

sized and promiscuous removal of supposed focal infections carried out. There is no doubt that these should be removed to promote the well being of the patient rather than for any influence their removal will have on the course of the bony degeneration.

### References

- Bauer J M and Freyberg R H Vitamin D Intoxication *J A M A* 130 1208 1946
- Dollings I Chronic Focal Infections and Their Etiologic Relations to Arthritis and Nephritis *Arch. Int Med* 484 1912
- Boorstein S W and Hirsch H Multiple Cartilaginous Exostoses With a Report of Two Cases *Am J Surg* 194 1949
- Brenckmann E, and Trentz F Exostoses Multiples Osteogenetiques Familiales A grand development ayant exigé plusieurs opérations *Rev d orthop* 16 333 1949
- Burke O R Hereditary Deforming Chondrodysplasia Three Cases in One Family *J Bone & Joint Surg* 11 570 1949
- Burton J A G Cowan J and Miller H Generalized Myositis Fibrosa With the Report of a Case *Quart J Med.* 17 103 1943 1944
- Cecil R L Rheumatoid Arthritis A New Method of Approach to the Disease *J A M A* 100 1220 1933
- Cecil R L and Archer H H Classification and Treatment of Chronic Arthritis *J A M A* 87 741 1926
- Cecil R L and Archer H H Arthritis of Menopause *J A M A* 84 75 1925
- Cecil R L Nicholls E E and Stainsby W J The Bacteriology of the Blood and Joints in Chronic Infections Arthritis *Arch. Int Med* 43 471 1949
- Cecil R I and DeGara I P The Agglutination Reaction for Haemolytic Streptococci in Rheumatoid Arthritis Its Significance in Diagnosis and Treatment *Am J Med Sc* 211 4 1946
- Cecil R I Hammerer W H and DePrume F J Goldsalts in the Treatment of Rheumatoid Arthritis A Study of 245 Cases *Ann Int Med* 16 611 1942
- Dawson M H Ohnstein M and Root R H Agglutination Reactions in Rheumatoid Arthritis *J Immunol* 23 187 1932
- Dietrich A Angeborene Knochenbrüchigkeit mit Besserung durch Vigantol *Virchows Arch f path Anat* 275 397 1930
- Fearing W Ritter & Dixon With Prolonged Auriculoventricular Conduction *Ann Int Med* 25 499 1946
- Feltz A R Chronic Arthritis in the Adult Associated With Splenomegaly and Leukopenia A Report of a Case of unusual Syndrome *Bull Johns Hopkins Hosp* 35 16 1924
- Fletcher Ernest Osteoarthritis An Attempt to Elucidate the Etiology and Pathogenesis of the Condition by Clinical Study and Analysis *Brit J Rheum* 2 62 1939
- Fletcher H M On Oxycephaly *Quart J Med* 4 383 1910 1911
- Graham D and Fletcher A A The Large Bowel in Chronic Arthritis *Tr A Am Physicians* 44 31 1909
- Hale L Hereditary Deforming Chondrodysplasia or Multiple Exostoses *Ann Surg* 92 94 1930
- Hench P S and Rosenberg H F Palandromic Rheumatism *Arch Int Med* 73 293 1944
- Jansen M Achondroplasia Its Nature and Its Cause *Leiden Brill* 1912
- Jansen M Dissociation of Bone Growth (Exostoses and Enchondromata or Other Dyschondroplasia and Associated Phenomena) *Jones Birthday Volume* 1928 p 43
- Kraus E J Osteogenesis Imperfecta und Endokines System *Virchows Arch f path Anat* 274 37 1929
- Marie P *Presse méd Paris* 8 17 1900
- Milani E Exostose Osteogenetische a Type Familiale Associate in un Caso con Allergioni Discondroplasiache Bilaterale *Arch. di radiol* 6 55 1930

back pain, lumbago or other indefinite syndromes. This signifies the importance of a detailed examination by x ray and other means to reach a factual diagnosis upon which will rest a rational therapy.

There is a group of cases of osteoarthritis which are thought to be associated with the menopause. There is little evidence to suggest that this is more than a coincidence, as osteoarthritis usually appears earlier in women than in men, and as at this time there is often a rapid increase in weight, and as the fifth decade is the period when the lesion is most commonly manifest, it is not at all surprising that this correlation suggests itself. The knees are most affected and many of these women have a faulty posture (high heels and bad shoes) and flat feet are common. The vertebrae and feet are also frequently involved but other joints may be affected. The symptoms are those already described for osteoarthritis and the x ray appearances are identical. The course of the disease is insidious and continuous, and although it may be arrested, regression never occurs.

*Senile or senescent arthritis* is merely a form of osteoarthritis. It is principally found in the spine, fingers and the larger joints of the arms and legs. It is indistinguishable from other forms of osteoarthritis except that it develops in the later decades.

Osteoarthritis of the spine or *hypertrophic spondylitis*, as it is sometimes called, is also a form of the same disease in which the principal bony changes are found in the vertebrae. It may give rise to considerable limitation of movement. It is otherwise symptomless unless the exostoses produce nerve pressure. The pain in these conditions has a spinal distribution. Very severe and agonizing pain may suddenly occur if through a sudden violent effort one of these exostoses is broken loose. It is surprising at times what a slight degree of muscular exertion may produce this. Other joints are usually also involved especially the hips and knees.

**Anatomical Changes**—The anatomical changes in osteoarthritis are purely degenerative, there being a progressive absorption and production of bone which leads to the distorted and irregular ossification about the joints. This is produced and aggravated by trauma either direct or from faulty posture. The joint cavity itself is practically never involved.

**Course**—The course is extremely insidious and although true ankylosis does not occur locking of the joint may result from impingement of the exostoses.

**Treatment**—The treatment is principally confined to the protection of the involved joints. This protection consists of the avoidance of trauma, and also in exercises which will improve the faulty posture. A reduction in weight in those who are obese is important to accomplish these ends and therefore the patient should be placed on a subcaloric diet. Thyroid extract potassium iodide, high vitamin diet and numerous other therapeutic procedures have been advocated but their effects are to say the least doubtful. Pain in the affected joints is often relieved by physiotherapy and particularly local heat. Massage and passive movements are to be used cautiously to avoid producing additional local trauma. The role of infections was at one time overempha-

## CHAPTER XVIII

### DISEASES OF THE URINARY SYSTEM

By WALTER D. M. SCRIVER, M.D.

#### Introduction

The diseases of the urinary system in the strict sense of the term should include all those abnormalities of structure and function which may be present from the glomerulus to the meatus, but from the point of view of the practice of medicine they are usually confined to lesions of the kidney and its pelvis which have an important influence upon the body as a whole. The more local lesions of the urethra bladder and ureters are dealt with in textbooks on urology. Normal renal function plays an important part in the maintenance of the internal environment, and any interference with its function produces widespread signs and symptoms. In fact many important diseases of this organ may be first suspected rather from systemic symptoms than from the local ones. Therefore it is important for a proper conception of renal diseases that its place in the general function of the body should be appreciated, rather than the narrower view of considering the organ and its functions as a separate entity. The examination of the urine gives important information as to the local anatomical changes occurring, but to assess its functional capacity general results must be investigated.

The anatomical and physiological unit is the nephron which in its simple form consists of a long tubule the upper end of which is invaginated by a leash of arterial capillaries (the glomerulus) the lower end of the tubule communicates with the collecting tubules which in turn empty into the renal pelvis. The glomerulus is closely surrounded by an epithelial layer (Bowman's capsule) which is the invaginated portion of the tubule. As the blood flows through the glomerular capillary it is thus brought into close contact with the membrane of the capsule through which it is secreted or filtered. (Present day theories favor filtration.) The amount and composition of the filtrate are thus dependent upon the amount of blood passing through the glomerulus the pressure of blood within the glomerulus and the osmotic pressure of this same blood. It is obvious that the state of the glomerular membrane itself will have a direct influence upon filtration. The filtrate has a composition similar to that of blood plasma minus the protein, whereas in the urine finally discharged from the kidney the individual substances may be concentrated to many times this original strength thus concentration (and possibly actual secretion) takes place in the tubules which also resorb water. All glomeruli are not in action at the same time leaving a large reserve to meet extra strain.

The function of the kidney thus in the final analysis depends primarily upon the glomerulus which furnishes the filtrate and secondarily upon the

- Miller, J L    A Critical Review of the Literature on Chronic Rheumatism, *Arch Int Med* 57 213, 1936
- Nicholls, E E and Stainsby, W J    Streptococcal Agglutinins in Chronic Infectious Arthritis, *J Clin Investigation* 10 323, 1931
- Pemberton, R    Diet in Treatment of Chronic Arthritis, *Am J M Sc* 161 517, 1921
- Pemberton R    Significance and Use of Diet in Treatment of Chronic Arthritis, *New York State J Med* 26 668, 1926
- Rankin, G and MacKay, E C    Achondroplasia, *Brit Med Jour* 1 1518, 1906
- Reiter, H    Ueber eine bisher unerkannte Spirochaeteninfektion (*Spirochaetosis arthritica*), *Deutsche med Wchnschr* 42 1535 1916
- Still G T    On a Form of Chronic Joint Disease in Children, *Medico chirurgical Soc. Tr* London 80 47 1897
- Stuckey E S    Dermatomyositis    A summary of the literature and the report of a case with commentary, *Brit J Dermat and Syph* 47 85 1935
- Suard P M E    Contribution à l'étude de la myosite aiguë suppurée, *Bordeaux*, 1817
- Weber M    Osteogenesis Imperfecta Congenita *Arch Path* 9 934, 1930



### Symptomatology

While extensive disease of the kidneys may exist without giving rise to symptoms there are nevertheless certain symptoms and signs the presence of which may be of significance. The most important include changes in the rhythm and volume of urination hematuria albuminuria edema headache pallor dyspnea nausea and vomiting twitching and convulsions and changes in acuity of vision.

**Changes in Rhythm and Volume of Urination—Frequency and Polyuria.** Frequency refers to the number of times the bladder is emptied. Except for habit spasm it is symptomatic of irritation of the renal pelvis or the bladder either from inflammation or other disease or from distention. In the absence of pathological irritation frequency is obviously closely related to the volume of urine secreted. Polyuria as its name implies refers to an increase in total volume; this may be associated with increased ingestion of fluid either as a voluntary effort or in diseases such as diabetes mellitus or diabetes insipidus. In renal disease polyuria has been explained as an attempt to excrete the waste products in dilute solution when the kidney has lost the ability to concentrate. Nocturnal frequency associated with nocturnal polyuria is suggestive of diabetes or renal disease rather than of a local lesion in the lower urinary tract.

Oliguria apart from mechanical causation is the result of decreased glomerular filtration due to any of the general or local causes discussed above.

**Hematuria** is significant of bleeding at any point along the genitourinary tract. As a rule the blood from glomeruli or tubules is intimately mixed with the urine which is voided giving it the smoky appearance long known to clinicians. In nephritis it is indicative of glomerular damage which allows the leakage of red blood cells into the lumen of the tubule.

**Albuminuria (Proteinuria)**—Though the proteins of the urine consist for the most part of albumin the term albuminuria is actually used in the broader sense of proteinuria. Albuminuria apart from that due to the presence of gross blood in the urine is evidence of an increase in the permeability of the glomerulus and Bowman's capsule to the larger protein molecules. This may be due either to circulatory or to inflammatory factors. Broadly speaking albumin is not a normal constituent of human urine though it may appear in normal people after heavy exercise or effort or sudden changes in circulation such as those caused by a cold bath.

**Casts** occur in the urine for the most part under conditions similar to those associated with albuminuria originating in the kidney; their base is thought to be of an albuminous nature. In general blood casts and epithelial casts are associated with acute infections granular casts with less acute stages and hyaline casts with the chronic state.

**Pus cells** in the urine are evidence of inflammation in any portion of the urinary or genital tract.

**Edema**—Edema is that condition in which there is present an excess of fluid in the tissue spaces within which it is relatively free to flow; under the influence of gravity it tends to collect in the lowest portions of the tissues. The process

tubules which work it up into the finished product excreted as urine. Generally speaking if the glomerulus fails, all the rest of that nephron fails also.

The functions of the kidney in general are

- 1 To eliminate water
  - 2 To eliminate salts
  - 3 To eliminate the waste products of nitrogenous metabolism
  - 4 To assist in maintaining the acid base balance of the organism
- } So preserving the salt and water balance

It is obvious that the secretion of urine may be influenced by numerous extrarenal factors, thus there may be a great decrease in volume when the body becomes dehydrated as from lack of fluid intake, or from loss of ingested

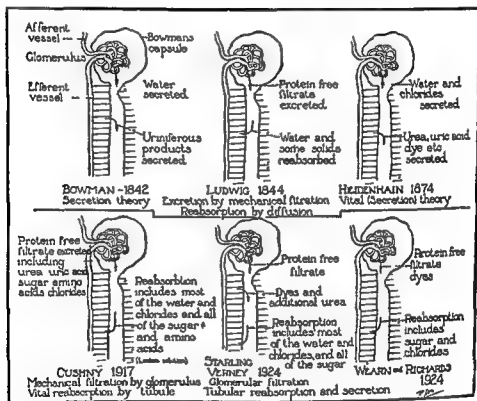


FIG 48—Schematic representation of various studies of renal physiology (P. A. Hench J. A. M. A. July 1926)

fluids in the sweat or vomitus or by diarrhea. With a failing circulation the pressure or blood flow within the glomerulus may fall to such a level as to be insufficient for filtration (this rarely occurs except in shock). In cardiac decompensation the added factors of asphyxia and tissue imbibition enter the picture. Extrarenal factors may also be responsible for changes in the osmotic pressure of the blood.

The intrarenal factors will fall roughly into three main groups—those changes which affect the circulation in the glomeruli such as thrombosis, diffuse or focal, changes in the epithelium of Bowman's capsule interfering with permeability, injury to the cells of the tubules below the glomerulus. It is evident that there may be a combination of several of these factors.

their original concentration. In human subjects this edema is seen in those conditions in which the total plasma proteins have fallen below the 'critical level' from chronic loss as in repeated hemorrhage, long continued serous discharges or massive albuminuria, from insufficient protein intake as in dietary deficiency, chronic diarrhea or other processes interfering with absorption or from chronic lesions which interfere with plasma protein formation.

As the albumin molecule exerts a much greater osmotic pressure than does the globulin molecule, losses of albumin are of greater significance and a low level of albumin in the plasma is apt to be associated with edema.

As would be expected in a systemic process, the edema produced by this means is generalized and clinically is usually severe and of the 'feather bed' type. It too may be most prominent in the soft parts and is apt to be associated with transudates in the serous cavities. The edema fluid will have a low protein content in contrast to that found in the first type of edema.

It is obvious that under certain conditions the ingestion of excessive amounts of fluids may cause edema through a similar process. Also the osmotic pressure may be built up in the tissues by salt retention and particularly by the sodium ion in which case the flow of fluid will again be from the vessels into the tissues. While the adrenal cortex appears to be a factor in the control of the sodium balance, our knowledge is not sufficient to explain the mechanism in this type of reaction.

It is doubtful if the third factor (increased hydrostatic pressure) ever acts alone to produce edema in the human body, but it is found frequently in combination with the other two mechanisms. A good example is the edema of the feet that comes on after long standing. Here asphyxia and interference with drainage of the tissue spaces also enter into the mechanism. The protein content of edema of this type will be influenced by the other factors.

**Passive Edema.**—The edema of poor drainage is bound up with the state of the capillaries and lymphatics and the venous blood flow. Anything tending to interfere with these will tend to produce edema. Pure passive edema is rare in practically all instances one or more of the active factors enters into the condition as well.

Other symptoms related to the *uremic state* are discussed below.

### Tests of Renal Function

With the better understanding of the physiology of the kidney it has become possible to devise tests which will show the total ability of the kidney to carry out its functions. In general these tests fall into one of two main groups:

1. The ability to excrete water and to concentrate normal products of excretion.

2. The elimination of foreign substances.

**I Concentration and Dilution Tests.**—In its simplest form this principle has been made use of clinically for many years in the examination of the night and the day specimens. Under average normal conditions the night urine will be of a dark color and have a specific gravity above 1.020.

may be divided into active and passive forms in the former there is an increased flow of plasma, or of certain of its constituents, from the vessels into the tissue spaces, in the latter the mechanism for the drainage of these spaces (via the lymphatics) is impaired

The active causes fall roughly into three main groups

1 Increased permeability of the vessel wall due to direct injury of the wall (The fluid "leaks" into the tissues)

2 Increased permeability of the vessel wall due to decrease in the osmotic pressure of the blood with corresponding decrease in the force holding the fluid within the vessels (The "thinner" fluid is drawn into the tissues)

3 Increased hydrostatic pressure in the vessels of the region involved (The fluid is forced into the tissues)

As a rule it is rare to find clinically an edema due to a single factor alone, usually at least two, and often all three of the factors are concerned



Fig 458—Photograph of a patient with the nephrotic syndrome to demonstrate general anasarca. Note the edema of face limbs and genitalia and protuberance of the abdomen with protruding of the umbilicus from a cello

A good example of edema due to injury of the vessel wall is that produced by certain snake (viper) venoms in which the capillaries become so permeable that the fluids of the blood escape in large quantities into the tissues Anoxemia also will produce this effect probably through changes in hydrogen ion concentration and cellular permeability In acute glomerulonephritis the causative factor is as yet unidentified being vaguely classified as toxic

Edema of this first type is usually diffuse in distribution and most severe in the soft parts where the histological structure permits a free distention of the tissues Such tissue is found particularly about the skin of the eyelids and the external genitalia

As might be expected the protein content of edema fluid of this type is relatively high, averaging 1 per cent or more

Edema of the second type can be produced experimentally in animals by the process of repeated plasmapheresis in which the blood is withdrawn and freed of the plasma proteins, the cells salts and fluids being re injected in

their original concentration. In human subjects this edema is seen in those conditions in which the total plasma proteins have fallen below the "critical level" from chronic loss as in repeated hemorrhage, long continued serous discharges, or massive albuminuria; from insufficient protein intake as in dietary deficiency, chronic diarrhea, or other processes interfering with absorption; or from chronic lesions which interfere with plasma protein formation.

As the albumin molecule exerts a much greater osmotic pressure than does the globulin molecule, losses of albumin are of greater significance, and a low level of albumin in the plasma is apt to be associated with edema.

As would be expected in a systemic process, the edema produced by this means is generalized and clinically is usually severe and of the "feather bed" type. It too may be most prominent in the soft parts and is apt to be associated with transudates in the serous cavities. The edema fluid will have a low protein content in contrast to that found in the first type of edema.

It is obvious that under certain conditions the ingestion of excessive amounts of fluids may cause edema through a similar process. Also the osmotic pressure may be built up in the tissues by salt retention and particularly by the sodium ion, in which cases the flow of fluid will again be from the vessels into the tissues. While the adrenal cortex appears to be a factor in the control of the sodium balance, our knowledge is not sufficient to explain the mechanism in this type of reaction.

It is doubtful if the third factor (increased hydrostatic pressure) ever acts alone to produce edema in the human body, but it is found frequently in combination with the other two mechanisms. A good example is the edema of the feet that comes on after long standing. Here asphyxia and interference with drainage of the tissue spaces also enter into the mechanism. The protein content of edema of this type will be influenced by the other factors.

**Passive Edema.**—The edema of poor drainage is bound up with the state of the capillaries and lymphatics and the venous blood flow. Anything tending to interfere with these will tend to produce edema. Pure passive edema is rare; in practically all instances one or more of the active factors enters into the condition as well.

Other symptoms related to the *uremic state* are discussed below.

### Tests of Renal Function

With the better understanding of the physiology of the kidney it has become possible to devise tests which will show the total ability of the kidney to carry out its functions. In general these tests fall into one of two main groups:

1. The ability to excrete water and to concentrate normal products of excretion.

2. The elimination of foreign substances.

**I. Concentration and Dilution Tests.**—In its simplest form this principle has been made use of clinically for many years in the examination of the night and the day specimens. Under average normal conditions the night urine will be of a dark color and have a specific gravity above 1.020.

the day specimen may be paler, and the specific gravity may be above or below that of the night specimen. This fact has been employed in more elaborate form in many ways.

**A The Two Hour Test (Modified Mosenthal Test)**—In brief the patient eats three ordinary meals but restricts the fluid intake to a total of 500 cc (two glasses) with each meal, no more fluid being allowed during the 24 hours of the test. From 8 A.M. to 8 P.M. of this day the bladder is emptied *completely* every two hours and the volume and specific gravity of each specimen are determined. All urine passed from 8 P.M. up to and including 8 A.M. next day is collected as a single specimen. Under normal conditions this night volume should not exceed 400 cc, and the specific gravity should be a minimum of 1.020. The individual day specimens should vary in volume, the total being about 800 cc, and the specific gravity should vary eight or more points ranging around 1.020.

With failure of renal function, the volume of the night specimen increases and the specific gravity decreases, when the latter is under 1.020, there is always a suggestion of impairment of renal function. In extreme renal failure the specific gravity of the individual specimens becomes fixed around 1.010, a sign of grave import. In acute renal failure the specific gravity may be low at first, rising with the resumption of secretion. In oliguria due to circulatory failure, with a normal kidney, specific gravity will be high ranging around 1.030.

**B Volhard's Concentration and Dilution Test** arrives at these results by withholding food and fluid from the patient after the evening meal until the next morning when he is made to drink 1500 cc of water. Urine is collected hourly for the next four hours during which time the normal kidney will excrete a dilute urine with a specific gravity as low as 1.001, and a total volume of approximately one liter. No further food or fluid is given, and further specimens are collected as voided during the day. By evening the volume should be low, and the specific gravity should have reached 1.020 or higher. With failure of renal function there is inability both to dilute and to concentrate the urine; the specific gravity of all specimens ranges closely around 1.010 in those cases in which little normal renal tissue remains.

A specific gravity of 1.010 to 1.012 is at the same level as that found in the plasma after the proteins have been removed which suggests that urine of this fixed specific gravity is but a dialysate produced by a kidney which has completely lost its power of concentrating the urine, a function of the tubules.

In both of these tests it is obvious that if the patient should happen to be excreting edema fluid at the time of the test, or should take extra fluid by mouth, the results will be fallacious. These sources of error should be watched for carefully in all tests.

**Urea Concentration and Clearance Tests**—As urea is a normal constituent of the urine it has been made use of as an index of the ability of the kidney to concentrate. Ambard's original formula has now been generally superseded by more modern versions. In *MacLean's concentration test* 15 grams of urea dissolved in 150 cc of water is given to an adult in the fasting state after

the bladder has been emptied. The urine is then collected at hourly intervals for two hours. Provided that the volume of the second specimen is not greater than 120 cc a normal kidney should excrete a urine containing a minimum of 2 per cent of urea. If the urea content of a blood sample taken at the end of the second hour be determined, Addison's concentration factor can be determined by the ratio

$$\frac{\text{Urea per cent in urine}}{\text{Urea per cent in blood}}$$

In a normal individual the factor should be above 35 and more usually 40 or above.

In *Van Slyke's urea clearance test* the patient may have breakfast and no urea is given. During the course of the morning two consecutive hourly specimens of urine are collected and a single blood specimen is taken before the end of the second hour. From these the 'standard' and 'maximum' clearances (blood cleared of urea) are calculated according to the urea content of blood and urine and the volume of the latter. Results are expressed as percentages of normal (maximum 75 cc per minute where volume of urine is above 2 cc per minute and standard 54 cc per minute where volume of urine is below this amount) according to the following formulae

$$1 \text{ Maximum clearance (per cent of normal)} = \frac{100}{75} \times \frac{U \vee}{B}$$

$$2 \text{ Standard clearance (per cent of normal)} = \frac{100}{54} \times \frac{U \sqrt{V}}{B}$$

**II Excretion of Foreign Substances**—Of all the tests based on the excretion of foreign substances the best known and most widely used is the phenolsulphonphthalein test often known as P.S.P. or 'red' test. In this case 5 mg. of the dye (1 cc. of the solution supplied in ampules) is injected into the lumbar or gluteal muscles and after ten minutes has been allowed for absorption specimens of urine are collected over the next two hours. These urines are then made strongly alkaline, diluted to a given volume and the colors are compared with a standard. The result is considered to be normal when from 60 to 85 per cent of the dye is excreted in two hours of which 40 per cent or more is passed in the first hour. In extreme renal insufficiency only a trace of dye may be present.

**Blood Chemistry**—Increase in the blood of those substances normally excreted by the kidney may give strong indirect evidence of renal insufficiency. Of the nitrogenous products the total nonprotein nitrogen should not exceed 30 mg. per 100 cc. by the original Lowry technique. Urea nitrogen should not be greater than 36 mg. per 100 cc. Creatinine is the last of the nonprotein nitrogen substances to increase and any rise in the level above the upper normal limit of 15 mg. per 100 cc. should always be considered significant. Similar levels, however, may be found in high intestinal obstruction.

U = Mg. per 100 cc. of urea in urine.

B = Mg. per 100 cc. of urea in blood.

V = Volume of urine per minute in cc.

As a decrease in the concentration of proteins in the plasma may be a factor in the production of edema, the determination of this level may be of importance. A total plasma protein below 5 per cent is usually associated with edema, particularly when the decrease has been so predominantly in the albumin fraction as to cause a reversal of the normal ratio of approximately 1.5 of albumin to 1 of globulin. As the level of cholesterol usually runs inversely to that of the proteins, an increase in this substance above the upper limit of 200 mg per 100 cc may also be of significance.

In advanced chronic renal insufficiency there may be an increase in the inorganic phosphorus of the serum, coincident with a decrease in the calcium. If the total proteins are low, the calcium may also be low due to decrease in the fraction bound to protein, but the inorganic phosphorus is usually found within normal limits.

TABLE XVI

COMPARISON OF FUNCTIONAL TESTS IN DIFFERENT RENAL STATES

	RELATIVELY NORMAL KIDNEY IN A CASE OF SIMPLE HYPERTENSION		GLOMERULONEPHRITIS WHICH HAS PASSED THROUGH THE NEPHROTIC STAGE		ADVANCED GLOMERULONEPHRITIS IN URÆMIC STATE	
	VOLUME C.C.	SPECIFIC GRAVITY	VOLUME C.C.	SPECIFIC GRAVITY	VOLUME C.C.	SPECIFIC GRAVITY
Two hour test						
8 to 10 A.M.	150	1.010	80	1.015	40	1.008
10 to 12 A.M.	50	1.018	40	1.017	30	1.010
12 to 2 P.M.	140	1.009	80	1.011	100	1.010
2 to 4 P.M.	70	1.016	100	1.010	90	1.010
4 to 6 P.M.	40	1.022	70	1.011	70	1.010
6 to 8 P.M.	40	1.024	100	1.011	220	1.010
8 A.M. to 8 P.M.	495	1.008	500	1.011	605	1.008
		1.024		1.011		1.010
8 P.M. to 8 A.M.	- 0	1.024	455	1.010	150	1.008
Urea concentra- tion and factor	2.7%	43.4	1.00%	22.2	Not done because of extreme urea reten- tion	
Urea clearance (Standard)	82.0%		38.0%		5%	
Phenolsulphon phthalein (Two hours)	80.0%		30.0%		Traces	

## BRIGHT'S DISEASE

Bright's disease is a somewhat general term which includes that disease group in which the kidney is the seat of progressive changes of vascular and inflammatory nature which changes are but special local manifestations of a more generalized process occurring in the body as a whole. It does not include the ordinary suppurative processes in the kidney nor tuberculous or syphilitic infections, but corresponds to the clinical entities included under the term 'nephritis'.

**Classification.**—The many classifications proposed have been the most potent source of the general confusion which has reigned in this field. The first grouping used was on a basis of morbid anatomy, such a classification is responsible for the terms 'large white kidney' etc. Later an attempt was made to classify according to the clinical symptoms and so we have such



descriptive phrases as chronic nephritis with (or without) edema, etc. In many cases there appears to be little agreement between the two. The better understanding of the physiology and pathological physiology of the kidney has served to make things more clear particularly so if we remember that the morbid anatomical specimen is merely a fixed point (the end stage) in a continuous clinical process which has led up to this point.

The clinical features which are used for classification are edema, hematuria and nitrogen retention. It is obvious that it will not be uncommon for two of these symptoms to be associated in the same case and all three may be present on occasion.

In general in relation to the pathological picture we find hematuria and nitrogen retention occurring where the glomerular lesion is the outstanding feature and edema when the tubule appears to be the most affected portion. Table XVII is an attempt to correlate some of the various classifications which have from time to time been put forward.

TABLE XVII

CLINICAL	CLINICOPATHOLOGICAL	CLINICOPATHOLOGICAL	PATHOLOGICAL
(Acute) hemorrhagic	(Acute) glomerulonephritis	Acute nephritis	Acute exudative (hemorrhagic) nephritis
Chronic nephritis with edema	Chronic nephrosis	Chronic diffuse nephritis	Large white kidney
Chronic nephritis with edema	Nephrotic state of glomerulonephritis	Chronic mixed nephritis (diffuse and interstitial)	Large → small white kidney
Chronic nephritis	Chronic glomerulonephritis	Chronic interstitial	Small white kidney
(Chronic) hemorrhagic	Chronic glomerulonephritis	Chronic interstitial	Primary contracted kidney
Chronic hypertensive			Small red kidney

**Etiology**—Clinical observations and experimental researches would suggest that there may be several factors which may be responsible for the development and progress of a nephritic process. These fall in general into three main groups: bacteria and their toxins, certain chemicals and progressive vascular changes.

Of the bacteria associated with nephritis the most common is the streptococcus; its primary focus frequently is in the throat as in tonsillitis and scarlet fever, though it may flourish elsewhere. *Staphylococcus* (from skin infections) and *pneumococcus* are less frequently concerned. While the colon bacillus is found frequently in pyelitis it is practically never directly concerned in the nephritic process.

The present tendency is to ascribe the local renal changes to an allergic response of the kidney to the infecting organism rather than to direct implantation of the organisms in the glomerular loop such as actually occurs in the focal nephritis of subacute bacterial endocarditis. In diphtheria where a severe acute glomerulonephritis may arise the process is due to the diphtheria toxin. Chemical nephritis is usually due to poisoning accidental or suicidal by some of the heavier metals of which mercury is by far the most common. The renal lesion in these conditions does not resemble patho-

logically that found in any of the other clinical types, and if the patient lives long enough, the kidney lesion heals completely

The vascular lesion which initiates the nephritic process may be secondary to an infection or toxin, or to the ordinary wear and tear phenomena which proceed in the vascular tree with increasing age. The role of focal infections in the production of nephritis is still not completely proved, such effects as might be ascribed to them have been mentioned above under bacterial and toxic factors

### The Experimental Production of Nephritis

Early attempts to produce nephritis in animals were all made by the administration of chemicals which have a direct toxic action on the kidney, those most used include mercury, uranium, and cantharides. The lesions produced in these experimental animals differ little from those which result in human subjects from toxic doses of the same drugs but in no case has there been any great similarity either in the complete clinical picture or in the pathological findings to those processes seen in human subjects suffering from Bright's disease

A condition of the kidneys which resembles closely, both in its clinical course, and in the pathological changes in the kidney, the chronic glomerulo nephritis which occurs in human Bright's disease has been produced by Hartmann, by exposing the kidneys of experimental animals to varying doses of x rays. These results are of great importance in stressing the essentially *vascular* nature of the process

The so called 'nephrotic' state has never been produced in animals by any experimental measures which result in a pure renal lesion. With the introduction by Leiter of the process of plasmapheresis whereby the plasma proteins can be reduced sufficiently to upset the osmotic pressure relations of the blood we are now able to produce at will in the experimental animal a massive edema which in practically all respects resembles that found in the nephrotic state without of necessity having an associated renal lesion

Smadel has produced nephritis experimentally in animals by the injection of nephrotoxins. These have been prepared by immunizing an animal of species B to extracts of kidney of species A and then injecting into an animal of species A the immune serum so produced. Similar results cannot be produced if the immunizing extracts are prepared from organs other than the kidney. The severity of the nephritis thus produced varies directly with the size of the dose of immune serum

It is of interest that, despite the apparent relationship of glomerulo nephritis to streptococcal infections attempts to produce an experimental nephritis by using injections of this organism have failed to give consistent results

### Glomerulonephritis

With the exception of certain chemical nephritides practically all nephritis is at some stage a glomerulonephritis. From the anatomical point of view this means interference with the blood supply of the glomerular loop, and the

convoluted tubules and from the physiological side implies an interference with the filtration process through the glomerulus and probably the secretion process in the convoluted tubules also. It is thus obvious that the extent of renal insufficiency will be directly proportional to the degree of involvement of the individual glomerulus and the number of glomeruli affected. As the outstanding pathological lesion is in the glomerulus so the outstanding clinical sign is hematuria. Associated signs may be those related to a general vascular lesion such as hypertension changes in the ocular fundus and in some cases edema.

### **Acute Glomerulonephritis** **(Acute Hemorrhagic Nephritis)**

The onset of this condition is frequently sudden during the course of an acute infection such as tonsillitis or pneumonia or some days after the apparent subsidence of the infection.

In many cases the patient awakens with swollen eyelids and face, and soon becomes edematous in all the loose tissues. The edema is apparently of the first type (discussed above) and may be so extreme as to close the eyelids completely. In the acute stages it is not usual to find fluid in the body cavities.

Coincident with the development of the edema there is an oliguria or actual anuria which may persist for several days. Such urine as is passed is dark in color and definitely bloody or with lesser amounts of blood smoky in appearance. Unless there has been previous failure of renal function the specific gravity is relatively high and albumin is present usually in large amounts. On microscopic examination numerous erythrocytes are seen many of which occur in the form of red blood cell casts coarsely granular and epithelial casts may also be present and leucocytes in numbers varying with the acuteness of the inflammatory process.

**Further Clinical Features**—Unless there has been previous cardiovascular disease the heart is not enlarged. The blood pressure however in the acute stages is increased and may at times reach approximate levels of 200 mg Hg systolic and 120 diastolic. The larger blood vessels show no signs of sclerosis or thickening but in the early stages occasionally the arteries of the fundus oculi can be seen to be greatly constricted while the veins are relatively full. In extreme cases hemorrhage and exudate may be present. There may also be a generalized contraction of the smaller vessels of the skin which assumes a pale appearance suggestive of anemia. The blood examination however may give a normal hemoglobin and erythrocyte count though the leucocytes may be increased.

The nonprotein nitrogen elements of the blood vary more or less directly with the degree of oliguria. In complete anuria they may rise rapidly to high figures to subside more slowly as the urinary output increases.

The acute stage may vary from a relatively small hematuria with little edema to an acute anuria with massive edema. It may be very short in duration with rapid subsidence and complete cure or may have a more gradual remission of symptoms with either complete cure or progress into the chronic state. In a certain number of cases the acute stage terminates in death within

a few days of the onset, this is more common in cases associated with diphtheria. With the remission of the oliguria large volumes of urine are secreted resulting in the subsidence of the edema. The hypertension gives way to a normal blood pressure level, and the ocular fundus resumes a normal appearance. Complete cure is not uncommon in children, but such a fortunate result is less frequent in adults in whom the subacute or chronic forms usually follow. Blood may continue in the urine in microscopic amounts for some days or weeks after the subsidence of acute symptoms. Its protracted appearance, however, is always highly suggestive that the condition has entered into the subacute or chronic stage.

As this condition progresses there is a gradual loss of renal function, often without symptoms until the well marked chronic stage is reached.

### Chronic Glomerulonephritis

Clinically this type is distinguished by progressive failure of renal function and increasing nitrogen retention with the symptoms related to this state. Anatomically the outstanding feature is the progressive destruction of the glomeruli and tubules with replacement by fibrous connective tissue which causes gross shrinkage of the organ eventuating in the terminal stage of 'small white (or red) kidney' (primary or secondary contracted kidney).

The etiological factors of this condition may be many or unknown, as stated above it may result from the continuation of acute glomerulonephritis, on the other hand it may appear quite insidiously with no recognizable preceding acute stage or infectious process. This type of renal lesion may be associated with the gouty diathesis or with chronic lead poisoning, occasionally it appears to follow on an apparently simple hypertension. Numerous attempts have been made to implicate excess protein diet, and particularly meat, as an etiological factor but clinical observation and experimentation have failed to bear out the results sometimes obtained in animal experimentation. While the chronic form may appear at all ages the majority of cases occur in later life particularly those with an insidious onset.

In the later stages the symptoms of both the so called primary and secondary forms are similar. In the early stages there are relatively few symptoms the persistence of albuminuria and particularly hematuria, may be the only finding to draw attention to the progressive feature of the once acute glomerulonephritis. The accidental discovery (as in examination for life insurance) of albuminuria may be the first sign that the "primary" process has begun.

In the early stages the most significant symptoms are those associated with the secretion of urine. With the decrease in actively functioning renal tissue, there is impairment in the ability to concentrate the waste products which are thus of necessity excreted in more dilute solution in the urine. In consequence it will take a larger volume of urine to keep the excretion of solids up to the necessary daily level and so polyuria and frequency result. As a rule the first increase is voided in the night urine which becomes progressively a larger fraction of the total 24 hour amount, at the same time the

specific gravity of the urine becomes lower in all specimens until ultimately it becomes fixed at a specific gravity of 1010 to 1012 which represents a simple protein free plasma filtrate with no attempt at concentration

The albumin content of the urine may at first be relatively large in amount, but as the disease progresses it decreases, and in the end stages may be merely a trace, though dilution may account for some of the decrease yet the total quantity is also decreased. Microscopic examination will always reveal red

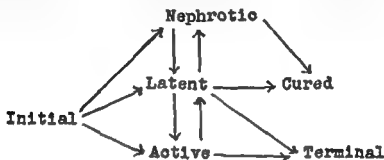


Chart XXXI—Diagrammatic scheme of progress of glomerulonephritis modified from Addi

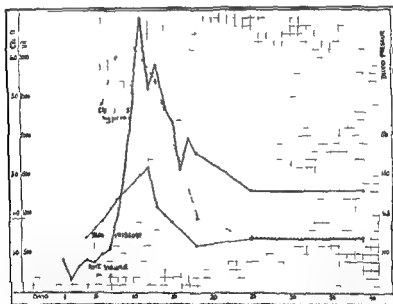


Chart XXXII—Creatinine showing rapid reduction of creatinine in acute anuria and return to normal with dialysis

blood cells though they may be very few in number particularly in the late stages. Casts at first are mainly of the coarsely granular and cellular type as the disease progresses they become more finely granular and ultimately are principally of the hyaline variety. Occasionally gross hematuria occurs associated with a flare up of the chronic into an acute or reactivated phase of glomerulonephritis. In this case unless there be a large amount of blood the specific gravity of the urine remains relatively low.

The level of the nonprotein nitrogen in the blood varies inversely with the ability of the kidney to concentrate. In the early stages it is within normal limits, but gradually it begins to increase from its level of 25 to 35 mg per 100 cc until in late stages it may reach as high as 200 mg per 100 cc. Of the individual substances the urea is the first to increase, and reflects slighter degrees of failure than does the creatinine which is the "last to go up" and when increased is evidence of severe renal failure. As the condition approaches the uremic state, the inorganic phosphorus of the serum begins to increase associated with a concomitant decrease in serum calcium.

Early in the process clinical symptoms may be absent, with the progress of the disease, apart from those definitely referable to the urinary tract (uremia), they fall into the groups referable to circulatory system and toxic changes.

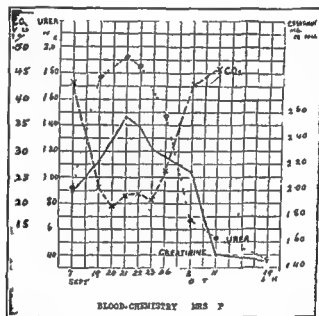


Chart XXXIII—Graph showing retention of urea and creatinine with associated acidosis in acute exacerbation of chronic nephritis with recovery of function.

Edema, which may be so prominent in the acute form usually does not appear until late and then in the dependent parts as it is referable to general circulatory failure. Occasionally there may be a slight puffiness about the eyes while the disease has still some of the acute features but this stage does not persist for long.

Hypertension develops relatively early in the process and continues throughout at first the systolic phase alone may be affected but later the diastolic level also rises the pulse pressure usually remaining fairly high. Coincidentally the thickness of the vessel wall increases (as found in the smaller arteries such as the radial) the thickening being more in the muscular coats and not of the calcareous plaque type met with in advanced arteriosclerosis. With the hypertension enlargement of the heart ensues chiefly of the "left sided" type. A systolic murmur may be heard due to relative mitral insufficiency. In some cases a fibrinous pericarditis develops as a terminal phenomenon.

In the retina there may be mild or advanced changes frequently the onset of visual disturbances is the first sign that draws attention to the true nature of the disease. In general the condition varies from early vascular changes to actual hemorrhage and exudate, and swelling of the disc. Although there has been a tendency to formulate the rule of death within two years of the onset of albuminuric retinitis, yet in individual cases there has been a complete clearing of the retina and slow progress of the renal condition.

As the disease progresses an apparent exophthalmos develops which may even suggest Graves' disease, but the pallor of the skin is in distinct contrast to the flushing seen in that condition.

The progress of the disease may be extremely slow, extending over years or it may run a fatal course within a year or so of the onset of the first symptoms. The ultimate termination is in uremia unless this event is anticipated by cerebral hemorrhage or thrombosis or cardiac failure, or by some fatal intercurrent infection.

### Nephrosclerosis

This term has been applied to that form of renal lesion in which the change is primarily in the afferent artery of the glomerulus rather than in the glomerular tuft itself. The symptoms are gradual in onset and often the first indication that the disease is present is the finding of albuminuria and hypertension at a routine physical examination. Unlike glomerulonephritis there is no history of infection at the onset and it also appears in later life usually from the fourth decade on. The clinical story of hypertension and renal failure is similar to that of chronic glomerulonephritis. While this is the 'small red kidney' of the pathologist as opposed to the 'small white kidney' of glomerulonephritis yet on occasion it may be impossible to diagnose the etiological factor from the morbid anatomy and histology alone and the clinical history is necessary to give the final diagnosis.

### The Uremic State

True uremia (literally 'urine in the blood') may be defined as that symptom complex which results from the retention within the organism of those substances which are usually eliminated in the urine. These include water inorganic salts nitrogenous waste products and certain organic substances. It will thus be evident that there may be several toxic factors and so the uremic state may express itself in several ways. Pseudouremic symptoms may be produced by local edema or circulatory changes in the brain arising either independently of or associated with the retention of toxic products, but it is now a generally accepted rule that there can be no true uremia except where renal function has so failed that nitrogen retention can be demonstrated in the blood.

This failure of renal function can be acute as in the case of sudden destruction or removal of the kidney tissue or chronic where the destructive process has gone on for months or years.

Uremia has been produced experimentally in animals by surgical removal of both kidneys thus preventing the formation of urine by the ligation of

both ureters, producing a similar effect slightly more slowly, and by damaging the kidney by poisons. All of these methods produce an acute uremia, which is not the type usually seen in clinical medicine. More recently the modern means of producing experimentally true progressive nephritis (x ray radiation) have succeeded in producing chronic uremia (see experimental nephritis).

The symptoms are not due to urea *per se*, for large doses of urea can be given such as will raise the urea in the blood to levels seen in the uremic state without producing similar symptoms. Likewise, other well known substances, such as uric acid and creatinine, have been shown to be relatively innocuous. If the total nonprotein nitrogen of the blood be determined in a normal individual and the nitrogen of all known nonprotein nitrogen substances be determined at the same time, it will be found that the sum total of the latter is not as great as the former, this difference representing unidentified substances called the "rest nitrogen." As nitrogen retention proceeds, with increasing amounts of nonprotein nitrogen in the blood, this rest nitrogen increases at a much greater rate so that in extreme retention it represents a large fraction of the total. There has been a natural tendency to consider that in this moiety is the substance—or are the substances—which account for the uremic syndrome.

It is also of significance to note the similarity of the symptoms occurring in hepatic failure to those seen in uremia. Indeed, at times they are liable to lead to mistaken diagnoses. The liver is an organ of detoxication and excretion, among other functions and failure of these functions results in the retention of toxic products. (See page 727.) A finding in uremia that suggests a link between the two conditions which as yet has not been satisfactorily explained is the occurrence of a positive van den Bergh reaction in the serum of uremic patients.

### Symptoms and Signs of Uremia

The majority of the symptoms and signs are due to irritation or depression of the central nervous system though they may manifest themselves in other organs both reflexly or directly. The most common symptoms are discussed below.

**Disturbances of the Sensorium**—*Idiopathic stupor*, and *coma* are usually produced by retained toxic substances especially the phenols, which depress the higher centers. The patient is drowsy and not interested in his surroundings, yet he will usually respond quite rationally when questioned, relapsing into the drowsy state when conversation ceases. Except in the terminal stages coma is rare.

**Restlessness and irrational states** obviously must be explained by a different mechanism here the cause is a poor circulation, from local vascular changes, or a generally failing circulation with the production of a mild degree of oxygen lack in the brain tissues.

**Visual Disturbances**—Often these are the first symptoms noted by the patient. They are commonly due to vascular lesions in the retina which have



been discussed above (page 1269). These lesions may also occur in 'pure' hypertension without renal disease and in the pre uremic state and so are not necessarily "true" uremic signs, they are however, usually present when the uremic state has set in.

**Headache** is commonly present, and is usually ascribed to 'toxic' products, but, it is often due to increased intracranial pressure associated with edema of the brain and particularly the meninges. In the former case the pain is dull and nagging, rarely acute and uninfluenced by posture, pain due to edema is usually more severe and is influenced by posture. The headache of pure hypertension is commonly worse in the morning wearing off as the day advances the uremic headache is present most of the time.

**Motor Phenomena**—Muscular twitchings are frequently present in the slowly progressing chronic uremic states and are practically never seen in those uremias which are of acute onset. They are usually seen as sudden contractions of individual muscles or muscle groups which follow no definite pattern and do not include purposeful movements. All reflexes are usually increased when twitchings are present.

These evidences of muscle irritability have been attributed to the low level of calcium in the blood plasma. The total serum calcium is frequently found to be low in the "nephrotic" state as well where no twitchings are observed whereas they may be present with a similar serum calcium value in uremia. This apparent discrepancy is explained by the level of ionised calcium in the nephrotic state it is normal whereas the amount of calcium bound to the plasma proteins is reduced because of the decrease of the latter. In the uremic state the plasma proteins are usually at a normal level with a normal amount of 'bound' calcium whereas the ionised calcium is decreased. This decrease in ionised calcium is directly dependent upon the increase in the plasma of the inorganic phosphorus associated with renal insufficiency.

It will be noted that the explanation of muscle irritability is reminiscent of that of tetany (see page 961) and so it is not surprising that the school that would ascribe the symptoms of tetany to guanidine should also account for those of the uremic state by an increase of guanidine in the blood due to failure of excretion. The chemical evidence for this however is not very strong.

**Convulsions** are probably rarely if ever due to toxic factors but to edema of the brain or local circulatory disturbances in such cases they are not primarily 'uremic'. However as both circulatory failure and edema are so frequently present with the toxic retention convulsions have usually been considered as expressions of the uremic state. They are usually severe and epileptiform in nature they may be single or multiple.

**Dyspnea** may be due to associated circulatory failure when it is apt to be paroxysmal and nocturnal if more severe periodic or Cheyne Stokes breathing may be a prominent feature. The dyspnea of pure uremia is due to acidosis associated with the retention of such acid radicals as chloride phosphate and sulfate and the loss of fixed base that occurs from failure

of the ammonia forming function of the kidney, and from loss of base in vomitus. The CO<sub>2</sub> combining power may reach such low levels as 10 volumes per cent.

This dyspnea is of the Kussmaul type, with strong and deep expiratory phase. (For further discussion of dyspnea see pages 323 to 331.)

Vomiting may be a very distressing symptom and at times may make it impossible for the patient to retain nourishment taken by mouth. Its causes are usually "toxic," operating by several mechanisms. (1) The vomiting center may be directly stimulated, (2) there may be local irritation of the gastrointestinal mucosa from ammonia formed by the breakdown of urea which is at high concentration in the tissues and is excreted into the gastrointestinal tract. In this respect it has long been held that the frequent finding of ulceration of the stomach, intestines and particularly of the colon at autopsy in this type of case is produced by a similar mechanism combined with local infarctions due to terminal vascular paralysis. Occasionally diarrhea occurs, due to the colitis so produced.

Loss of weight and general wasting are present in all cases of chronic uremia though they may be masked by edema. The obvious cause of the undernourishment is the lack of sufficient caloric intake and absorption, due in turn to several factors of which anorexia, nausea and vomiting are the most important. With the lack of sufficient fluid intake the patient may become extremely dehydrated. In addition to the evidences of this state seen in the skin and subcutaneous tissues, the tongue is dry and beefy in appearance. Acute parotitis, probably due to infection spreading up the ducts from the mouth is a not infrequent terminal complication which precedes death by but a few days.

Pallor is practically always present. It has a dual origin: (1) actual anemia which has been shown to be due to a depression of the bone marrow; (2) a smaller vascular bed due to "shutting down" of the capillaries of the skin with a consequently smaller amount of oxyhemoglobin per unit of area to color ("Pale hypertension" of Volhard).

Ecchymoses are frequently found on the limbs, less frequently on the body and rarely on the face. They are due to increased permeability of the vessel walls, terminal vascular paralysis and changes in the blood itself caused by the retention of toxic products.

Epistaxis is frequent from infarction and ulceration of the nasal septum. The bleeding point usually is easily found on the septum not far from the external opening of the nares and is better treated by local styptics or cauterization than by diffuse pressure.

Occasionally skin irritation occurs as an intractable pruritus. This has been ascribed to the formation of ammonia from the urea which is excreted in the sweat and deposited as a "frost" on the skin where it decomposes.

### The Nephrotic Syndrome

Probably no division of Bright's disease has caused so much controversy or confusion as that classified under the head of "nephrosis." The original diagnosis was based on a purely pathological viewpoint and referred to the

condition in which the tubules alone appeared to be affected, the glomeruli and blood vessels being free. By far the majority of cases are of the mixed type, that is, both clinically and pathologically they show evidences of the nephrotic and glomerulonephritic state. The author is of the opinion, along with many others, that the so called 'pure' nephrosis is relatively rare and that if many cases so diagnosed were only followed carefully for a sufficient length of time evidences of glomerulonephritis would ultimately be found. To avoid confusion we shall first discuss the so called *pure nephrosis*.

The etiology is uncertain, frequently there is a history of an antecedent infection of the upper respiratory tract. In many cases there has been malaise often with fever which has been diagnosed clinically as influenza or grippe. Infection of the paranasal sinuses was much stressed at one time as the actual cause. In the majority of cases however it is difficult to find a definite etiological factor.

The outstanding clinical features are edema and heavy albuminuria. At the onset the edema is usually slight, beginning in the feet and gradually extending up the legs; later it develops into a general anasarca with soft pitting edema over the whole body, including the face and a large amount of fluid in the serous cavities. The swelling of the genitalia may be so great as actually to render urination extremely difficult; the fluid in the serous cavities may give rise to respiratory and cardiac embarrassment. This edema usually develops slowly, in contrast to that found in acute glomerulonephritis and may persist for months. At times it may disappear rapidly, but as a rule the subsidence is a slow process. As already stated, there is a massive albuminuria though this is the urine which is familiarly reported to 'boil solid'; yet the actual protein content rarely exceeds 2 per cent. The specific gravity is usually close to 1.020 and in the microscopic examination no red blood cells are found though casts are present in variable numbers. The casts include granular and hyaline types and rarely cellular varieties; if the polarized light be used many are seen to contain doubly refractive globules which also may be present free in the urine; these are the lipoids which Munk feels are specific of the disease process.

*The blood serum is milky in appearance as originally described by Bright.* There is no nitrogen retention but the total protein content of the plasma is lowered, the loss being almost wholly in the albumin fraction due either to impaired formation or/and to urinary protein loss. This lowering of the plasma colloids is the chief cause of the massive edema as discussed above. In addition there is a large increase in the cholesterol in the blood and a lowering of the calcium due to decrease in that portion bound to the proteins.

In the pure nephrosis these comprise the total abnormal clinical findings. The heart, blood vessels and blood pressure are normal; the fundi show no changes in the vessels and no hemorrhage or exudate though there may be some edema of the retina.

The various tests of renal function give good results and the whole picture is more one of water retention in the tissues than of renal failure. Epstein has called the condition 'diabetes albuminuricus' and ascribes the

of the ammonia forming function of the kidney, and from loss of base in vomitus. The  $\text{CO}_2$  combining power may reach such low levels as 10 volumes per cent.

This dyspnea is of the Kussmaul type, with strong and deep expiratory phase. (For further discussion of dyspnea see pages 323 to 331.)

**Vomiting** may be a very distressing symptom and at times may make it impossible for the patient to retain nourishment taken by mouth. Its causes are usually "toxic," operating by several mechanisms. (1) The vomiting center may be directly stimulated, (2) there may be local irritation of the gastrointestinal mucosa from ammonia formed by the breakdown of urea which is at high concentration in the tissues and is excreted into the gastrointestinal tract. In this respect it has long been held that the frequent finding of ulceration of the stomach, intestines and particularly of the colon at autopsy in this type of case, is produced by a similar mechanism combined with local infarctions due to terminal vascular paralysis. Occasionally diarrhea occurs due to the colitis so produced.

**Loss of weight and general wasting** are present in all cases of chronic uremia, though they may be masked by edema. The obvious cause of the undernourishment is the lack of sufficient caloric intake and absorption, due in turn to several factors of which anorexia, nausea and vomiting are the most important. With the lack of sufficient fluid intake the patient may become extremely dehydrated. In addition to the evidences of this state seen in the skin and subcutaneous tissues, the tongue is dry and beefy in appearance. Acute parotitis probably due to infection spreading up the ducts from the mouth is a not infrequent terminal complication which precedes death by but a few days.

**Pallor** is practically always present. It has a dual origin. (1) actual anemia which has been shown to be due to a depression of the bone marrow. (2) a smaller vascular bed due to "shutting down" of the capillaries of the skin with a consequently smaller amount of oxyhemoglobin per unit of area to color ("Pale hypertension" of Volhard).

**Ecchymoses** are frequently found on the limbs less frequently on the body and rarely on the face. They are due to increased permeability of the vessel walls, terminal vascular paralysis and changes in the blood itself caused by the retention of toxic products.

**Epistaxis** is frequent from infarction and ulceration of the nasal septum. The bleeding point usually is easily found on the septum not far from the external opening of the nares and is better treated by local styptics or cauterization than by diffuse pressure.

Occasionally skin irritation occurs as an intractable pruritus. This has been ascribed to the formation of ammonia from the urea which is excreted in the sweat and deposited as a 'frost' on the skin where it decomposes.

### The Nephrotic Syndrome

Probably no division of Bright's disease has caused so much controversy or confusion as that classified under the head of 'nephrosis'. The original diagnosis was based on a purely pathological viewpoint and referred to the

may develop while the edema is still present and the patient may even have an increasing systolic blood pressure and nitrogen retention at this time. Ultimately the edema regresses and the picture is that of advanced glomerulonephritis as outlined above, with none of the features typical of the nephrotic state.

It must be borne in mind that death may take place at any stage in the procession of events, and so the actual picture in the kidney can vary from pure nephrosis with much tubular degeneration and lipoid infiltration but relatively normal glomeruli to the secondary contracted kidney as discussed above. Many patients die of pneumococcal peritonitis.

### Intercapillary Glomerulosclerosis

In the chronic diabetic whose condition has been inadequately controlled over several years there may develop a clinical picture which closely resembles that of the nephrotic state characterized by edema often massive in extent, albuminuria, hypoproteinaemia, hypertension and retinal lesions of varying degrees of severity. The condition progresses with increasing nitrogen retention and usually ends in uraemia within a year or two of the onset of symptoms unless a vascular accident anticipates this ending.

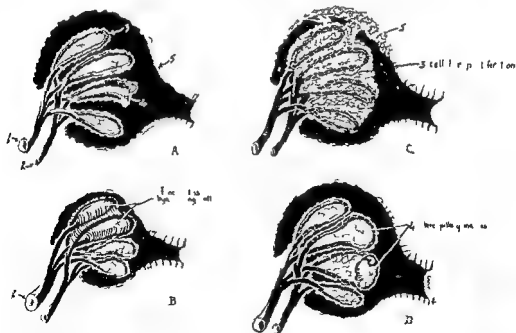


Fig. 460. A diagrammatic representation of the location of the lesion in certain renal disorders.

A Normal glomerular tuft and circulation. (1) afferent arteriole, (2) efferent arteriole, (3) glomerular capillary tuft, (4) intercapillary space, (5) Bowman's capsule.  
 B Arteriole sclerosis. Note the primary lesion in the afferent arteriole (1) which is a thickening of the wall and narrowing of the lumen, the eventual obliteration with consequent functional hyaline tufts.  
 C Glomerular nephritis. Note that the lesion is in the glomerular tuft (3) and Bowman's capsule (5) with cellular proliferation and adhesion with eventual degeneration of the tuft.  
 D Intercapillary glomerular sclerosis. Note that the lesion is in the intercapillary space (4) leading to tuft compression and obliteration of the glomerular tuft.  
 (Court, J. D., Syd., Freeman.)

sequence of events to a primary loss of proteins in the urine through some little understood metabolic upset, with relatively little renal disease

An interesting feature of many of these cases is that their basal metabolic rate runs at a low level a rate which is still low even when allowance is made for the edema weight. It requires large doses of thyroid substance to produce any effect in raising the rate. During the active process the patient is more susceptible to infections, particularly by the pneumococcus, which not infrequently sets up a peritonitis in the ascitic abdomen as a terminal complication

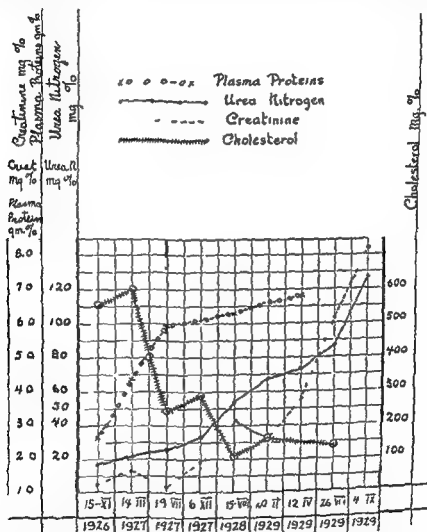


Chart XXXI. — Composite curve of blood urea and creatinine plasma proteins and cholesterol over a period of three years showing change from the nephrotic state to that of severe nitrogen retention

By far the majority of these cases of nephrosis occur in children in whom the disease may frequently proceed to complete healing with gradual or rapid loss of edema ultimate clearing of the albuminuria and restoration of the blood to the normal chemical state. On the other hand a large number of apparently pure nephrosis cases ultimately take on the signs of glomerulo-nephritis as evidenced by the findings of red blood cells in the urine the gradual increase in blood pressure and changes in the fundi. These signs

assimilated. With both milk and fruit juices the total fluid intake should be watched and adjusted to the occasion. This regime will be found much more acceptable to the patient than the so called 'thirst cure' and usually gives equally as good results.

In the stage of acute oliguria no attempt should be made to supply more fluid than is necessary to replace that lost through the skin, lungs and digestive tract. As a general rule the average adult may be given each day a total volume equal to the urine output of the previous day plus 1000 cc. If vomiting should be severe this amount should be increased correspondingly. Diuresis cannot be forced by loading the body with fluid which it is unable to excrete and such extra fluid in the tissues may actually do harm by producing edema of the brain and other vulnerable tissues.

Chlorides should be replaced in accordance with the loss of this ion in the vomitus, sweat and other fluids. In any prolonged state of oliguria the daily determination of the chloride level in the plasma is almost an essential in determining proper treatment.

The addition of glucose in 5 or 10 per cent concentration to the fluid given intravenously will serve to supply an available carbohydrate as a source of nourishment.

With the subsidence of the acute stage, more solid articles of diet can be added such as cereal, milk and milk puddings, toast, cooked fruit, baked or mashed potato. Later the higher protein foods can be added. Chicken, fish, and meat have relatively similar protein content and according to recent observations, have little injurious effect on the kidney even in acute stages. As chicken is relatively more bulky, a given weight will appear much larger to the patient than the corresponding weight of red meat.

With the chronic or subacute stage a more permanent dietary regime can be instituted. On the whole the tendency in the past has been to cut the protein intake too drastically. With insufficient intake the body proteins may break down leading to loss of weight and adding to the nitrogen available for urinary excretion. If the protein deficit be spread over a long period actual depletion of the body reserves and finally of the plasma proteins may follow so inducing the nephrotic state and its associated symptoms.

Thus there can be no hard and fast rule for diet in chronic cases. The protein intake should be varied to fit the individual case. When there is no marked increase in the nonprotein nitrogen of the blood it may be sufficient to restrict the protein by allowing a small serving of chicken, fish or meat once daily, to limit eggs to one a day and milk to not more than one glass a meal. Cheese as a high protein food may be used as a substitute for egg or meat. One cubic inch of the yellow domestic variety is the equivalent of one egg or half a meat serving. In the presence of an advanced degree of nitrogen retention the protein content of the diet should be reduced to the minimum. Often this is achieved automatically by the patient's symptoms but where it is not a diet of the type suggested for the acute stages is more suitable.

High protein diet is indicated in the nephrotic syndrome when the plasma proteins are at a low level. To obtain a high intake which should average

The lesion found in the kidney is distinctive as first described by Kimmelstiel and Wilson, in the nature of a fibrous tissue proliferation between the loops of the glomerular capillaries leading gradually to a complete replacement of the functioning glomerulus and loss of the corresponding nephron

### Vascular Renal Failure

The kidney requires a good circulation of blood in order to carry out its function. Experimentally any interference with outflow from the renal vein will tend to produce a heavy proteinuria, if long continued, or severe, casts and even red blood cells may appear in the urine.

In circulatory failure if the kidney be relatively normal, these same factors hold. The volume of urine is decreased, such as is secreted has a high specific gravity (about 1.030) contains a fairly large amount of protein and casts, usually of the granular variety, red blood cells are rare. In severe cardiac failure there is frequently a moderate rise of the nonprotein nitrogen in the blood, values as high as 60 mg per 100 cc are not uncommon, these return to normal limits as the circulation improves and more urine is excreted. Creatinine values however rarely exceed normal limits.

Frequently the question may arise as to whether we are dealing with a circulatory failure, secondary to chronic renal insufficiency, or with a primary circulatory failure with secondary renal manifestations. In these cases the specific gravity of the urine is all important, the badly damaged "chronic" kidney cannot concentrate urine, and so no matter how great the circulatory failure, the specific gravity of the urine still remains low (approximately 1.010 to 1.015). On the other hand, the normal kidney will respond to the circulatory failure by concentrating the urine to the high levels of specific gravity mentioned above. In very acute renal failure, the specific gravity may be high, but many red blood cells and leucocytes will be found in the urine.

### Treatment of Nephritis

Preventive measures must of necessity be very general in nature. These include the avoidance of exposure to the elements and to infection and the proper care of any infection once initiated. A warm climate with no sudden changes of temperature is most advisable but as very few patients can afford to move to such a region if they do not already live there they should be protected against the variations of the weather. This is best carried out by wearing woolen underwear, which will absorb perspiration and prevent "chilling" in winds or after exertion as it can be procured in light weights for hot weather it may be worn the year round. Similarly wet feet, damp shoes and stockings, etc. should be guarded against and changes to dry clothes made as soon as possible.

**Diet**—In acute nephritis with oliguria or anuria, the general principle is to give a diet which is easily assimilated, contains little or no nitrogen and has a relatively low salt content. The fruit juices answer these requirements best, and are usually most acceptable to the patient. Despite its widespread use, a pure milk diet is not theoretically as useful, as it contains approximately 3 per cent of protein and a relatively large amount of salts, and is not so easily



**Edema**—Appropriate treatment obviously demands a diagnosis of the causative factor and measures directed toward its alleviation or cure.

For the edema associated with acute glomerulonephritis, the so called thirst cure has been recommended. In the strict form no fluids are given until urinary secretion has been resumed a procedure which involves great suffering by the patient. In a less severe regime the fluids are cut down rigidly to an absolute minimum of varying amount. With the resumption of secretion a diuresis usually results which clears the body of the excess edema fluid and the intake can be correspondingly increased.

The edema of the nephrotic syndrome is usually extremely resistant to treatment yet frequently spontaneous improvements occur which have no apparent definite relation to any of the therapeutic measures in force at the time. In general it is wise to balance the fluid intake against the output as the urinary excretion is low. A 24 hour intake of 800 to 1000 cc (approximately 4 to 5 glasses) is usually sufficient. (See also the Schemm regime above.) In theory a high protein diet is indicated as outlined above. If repeated analyses of the blood are made the nonprotein nitrogen will often be seen to rise after the high protein diet has been taken for some time. This should not necessarily be taken as a sign of increased renal failure unless the creatinine also is appreciably elevated. An increase in nonprotein nitrogen alone is frequently seen and is probably due to the split products of the food proteins in transport to the process of building up the specific body proteins. This diet must be continued for many weeks before the proteins will be restored to normal levels. Salt restriction has been discussed above. Occasionally a change of diet to one composed of fruit juice or milk will give a greater general restriction of both fluids and salt than has previously been obtained.

The use of diuretics should be considered carefully for each individual case, with particular care for those which are direct renal irritants. Urea will occasionally produce sufficient diuresis to reduce edema. Obviously it will be useless in those cases where there is already a considerable urea retention in the blood. In other cases it should be given in sufficient dosage to produce a "head" in the blood stream e. g. 15 grams or more every 3 or 4 hours for five doses.

The acid producing salts occasionally are useful in initiating diuresis though as a rule they are apt so to irritate the stomach as to induce vomiting. Ammonium chloride 1 gram in water every hour for six doses is usually sufficient to produce an effect if it is to be obtained. This drug can now be obtained as an enteric coated tablet.

The mercury diuretics such as salyrgan neptal etc. have been advocated in the nephrotic state particularly in combination with the acid producing salts. In the author's opinion drugs of this type are dangerous in practically all types of Bright's disease and if they are used daily urinalysis and microscopic examination should be made so that signs of renal irritation may be observed at an early stage and the drug be discontinued before severe damage is done.

Because of the low basal metabolic rate that is frequently found in the nephrotic state thyroid and thyroxin therapy have been used. These patients

125 grams of protein or more daily, will necessitate the use of meats fish eggs cheese and milk in large quantities

Vegetables are relatively low in nitrogen except peas and beans and as nitrogen in these latter is not readily available for body building they are better omitted from the dietary. Asparagus gives rise to hippuric acid a possible renal irritant and so likewise it should be omitted. Most of the fruits can be taken freely, but as plums (including prunes) and cranberries give rise to benzoic acid also a possible renal irritant they are better omitted from the diet. While the ordinary cereal products contain proteins, their use in moderation is permissible. On general principles it is wiser to omit rich puddings and pastries. The use of spices should be discouraged as there is sufficient reason to believe that these substances may be irritating to the inflamed kidney. Pepper, mustard catsup, etc., are obvious sources less obvious are some of the candies, or soft drinks such as ginger ale which may contain very little ginger but an appreciable amount of capsicum a definite renal irritant.

Although salt is not properly a spice, it is usually considered with the condiments. When edema is present it is wise to restrict the salt intake, the sodium ion is the one which helps hold water in the tissues. Even in the nephrotic state where there may be a relatively good excretion of salt ingested its restriction often favors the excretion of greater amounts of fluid from the body stores with a corresponding diminution in edema. This principle is the basis of the treatment advocated by Schenck who prescribes a salt free diet and at the same time forces water intake even up to 10 liters daily. While many cases of edema notably those of cardiac type (see page 367) improve under this therapy yet a truly salt free diet is most unpalatable and can rarely be prepared outside a special diet kitchen. However if free salt be forbidden at the table and only a moderate amount be used in the cooking, favorable results may be obtained. The use of salt substitutes will thus be unnecessary. Several of these have excluded the chlorine ion but still retain the sodium ion which is the one more intimately concerned with water retention. Closely related to this type of treatment is the so called rice diet which has been brought forward by Kempner principally in the treatment of hypertension. Its chief value would appear to be in its low sodium content but it soon becomes monotonous and is not adapted to long continued treatment.

Soups are usually a great source of salt in addition to their high content of nitrogenous 'extractives' if they have been made from meat stock. As none of these has any food value and the path of excretion is through the kidney the exclusion of 'clear' soup from the diet would seem logical. Simple purées however with no base of stock may be allowed.

Tea coffee and cocoa all contain some of the xanthin diuretics which act by direct irritation of the renal epithelium their use therefore becomes undesirable on general grounds. However if the patient appears to suffer from their deprivation he may be allowed one cup of weak tea or coffee at a meal. The use of substitutes must be considered according to the merits of the beverage and the patient's desires.

**Convulsions**—Convulsions if severe must be treated by the administration of strong sedatives such as chloral hydrate by rectum or sodium amytal intravenously. The use of chloroform by inhalation is not advisable if it can be avoided. Where the convulsions are related to edema of the brain, the intravenous injection of 10 cc of a 25 per cent solution of magnesium sulfate may be very efficacious, in such a case a 10 per cent solution of a calcium salt such as the gluconate should be ready for immediate injection in case of magnesium shock. Equally good results, without the danger of shock, can be obtained by the use of intravenous injections of hypertonic sugar solutions, the usual amounts given are 100 cc of a fifty per cent glucose solution, or 150 cc of a twenty five per cent sucrose solution.

The twitchings seen in the course of uremia are usually more annoying to the members of the patient's family than they are to the patient. Because of their relation to the diminution of ionized calcium in the blood it would seem logical to give calcium intravenously, as in the form of a ten per cent solution of calcium gluconate. The results, however are disappointing as the amount of ionized calcium changes very little in the presence of the hyperphosphatemia.

### The Artificial Kidney

All of the procedures outlined above have been in the ultimate analysis attempts either to restore kidney function or to reduce the concentration in the tissues of those products of body metabolism which the kidney is failing to excrete.

From the consideration that the kidney is in general a dialyzing membrane there arose the concept that other semipermeable membranes of the body might be made to act vicariously. Accordingly there was developed the procedure of peritoneal lavage at first intermittent later continuous with favorable results in some cases. Such a method has obvious limitations many difficulties and is not without danger.

The principle of actually dialyzing the patient's blood against Ringer's or other solutions has recently been developed to a point where the artificial kidney is now a recognized therapeutic instrument. With this type of treatment many grams of nitrogenous and other waste substances can literally be washed out of the blood stream and tissues after a few hours of treatment the high nonprotein nitrogen of the blood can be reduced to a normal level. The whole procedure in practice is complicated and requires trained personnel to carry it out but it may be the means of saving a life in cases where the renal failure is of a temporary nature from which the patient can recover if he is not allowed to die of uremia in the meantime.

### Renal Rickets

This is a form of chronic nephritis which occurs in children in which the features are those of chronic glomerulonephritis associated with dwarfism and rachitic changes in the bones. The disease begins in infancy or early childhood and may last for several years ultimately ending in death with uremic symptoms or from some intercurrent infection. The nephritic symp

are extremely resistant to such preparations and may often require 3 grains or more of thyroid extract daily without showing toxic effects or, indeed much change in the basal metabolic rate

The treatment of the edema of circulatory failure occurring in the course of renal disease should follow the outline presented in that section

**Anemia**—As a rule the anemia of nephritis is secondary to a depression of bone marrow activity. The exhibition of iron in various forms may be followed by some improvement in the blood picture, Basham's mixture has long been a favorite form of administration. Blood transfusions have relatively transient effects and are not of great use.

**Vascular Renal Failure**—Here the treatment obviously depends on restoration of the local and general circulation. These measures have been discussed elsewhere (see page 364)

**The Uremic State**—The type of diet that is indicated in this state has been discussed above.

**Headache**—In the early stages headache may be the main symptom. If it be due to edema of the brain the measures discussed above for the treatment of edema may give some relief. The 'toxic' headache associated with nitrogen retention may respond to the general measures, or it may be necessary to use added drug therapy. Tablets or capsules of the popular combination of acetyl salicylic acid with caffeine and phenacetine, and in severe cases codeine, usually will be helpful and unless they are taken in large numbers the theoretical bad effect on the kidney can be neglected. Lumbar puncture may be tried in severe cases and frequently affords prompt relief.

**Vomiting**—If vomiting is severe, gastric lavage may give some relief, it is well to remember however, that the gagging and struggling associated with the passage of the stomach tube may raise an already high blood pressure to dangerous levels, in which case the nasal tube may be less objectionable. When vomiting is prolonged fluids are best administered intravenously. Originally it was believed that hypertonic glucose solutions might 'force' a diuresis but this has not been borne out in practice. The glucose however is a source of energy for the body and if it be given in 20 per cent solution a relatively large amount can be given in a volume which is not too large. Frequently an intravenous injection of 300 cc of 20 per cent glucose saline twice daily will make the patient feel much more comfortable.

In addition to the above procedures, high colonic irrigation with warm or hot tap water may be tried once or twice daily according to the strength of the patient. It is thought that nitrogen elimination by the bowel is encouraged in this way. Sweating has fallen into disfavor as its physiological effects are better understood. It has been shown that the nitrogen and salt content of the sweat is relatively low the water high consequently the effect of a successful sweat will be actually to concentrate presumably the 'toxic' substances, the nitrogen and salts in the body tissues and blood stream. As an edematous patient rarely can be induced to sweat profusely, this method is not of much use in aiding the elimination of edema fluid.

### **Amyloid Disease of the Kidney**

Amyloid is deposited in the kidney as in other organs during the course of certain chronic cachectic diseases such as tuberculosis, syphilis, and prolonged suppuration.

The amyloid kidney may be normal in size or moderately enlarged, and on section appears lardaceous. The amyloid is deposited in and about the capillaries and small arteries, as in other organs; consequently glomeruli so affected may be destroyed with subsequent degeneration of the tubule.

The symptoms are similar to those observed in the nephrotic syndrome with massive albuminuria followed by edema; while the loss of protein in the urine is one cause of the lowered plasma proteins, there may also be a poor absorption of proteins in the diet if the intestinal tract is also involved by the amyloid condition, or if diarrhea be a prominent feature. Prolonged suppuration also causes a considerable loss of protein to the body.

Treatment involves the removal of the cause if possible, the attempt to furnish a high protein intake, and the general treatment outlined for the nephrotic state. On the whole the prognosis is poor though death may not follow for several years after the onset of renal symptoms.

### **Congenital Polycystic Kidneys**

This condition resembles closely in its clinical picture that of advanced glomerulonephritis with its hypertension and vascular changes and signs of renal insufficiency. Palpation of a mass in the region of one or both kidneys should always excite suspicion of this condition in the presence of the other signs. A ray may be of aid in demonstrating the large kidney mass if palpation is difficult.

The majority of these patients die before their fortieth year, though occasional cases may be found later in life. The treatment is similar to that outlined for chronic nephritis.

### **Congenital Aplasia of the Kidney**

While congenital aplasia of the kidney is not a common lesion yet its occurrence is of sufficient frequency to warrant its consideration as a possible contributing factor in advanced degrees of renal failure.

Its presence may be suspected in those cases of Bright's disease (and of surgical conditions of the kidney) in which there is a rapid failure of renal function which is out of proportion to what might be expected from the history and clinical findings. The actual diagnosis will depend upon the demonstration of the condition by pyelography or at operation or autopsy.

The defect in development is more common on the left side, where there may be either no demonstrable kidney tissue, or a small undeveloped mass of rudimentary kidney tissue. The ureter also may be absent, rudimentary, not patent or much dilated with or without stricture. The condition is perfectly compatible with life and good health as long as the other kidney is normal, but with its loss of function symptoms develop rapidly.

The treatment is that indicated for the remaining kidney.

toms are similar to those seen in the glomerulonephritis of adults except that hypertension is rare, at least until late in the disease. The bony changes are probably related to the upset in calcium and phosphorus metabolism which is found in the advanced nephritic state (see above). Infantilism may be a prominent feature, but as death takes place before puberty or soon after, it is usually not as marked as the other associated conditions. The treatment is similar to that outlined for chronic nephritis, modified where necessary to fit the age of the patient.

### Orthostatic Albuminuria

Orthostatic albuminuria is a condition occurring chiefly in children and occasionally in young adults, in which albuminuria is present intermittently without the presence of renal or urinary tract disease. The albumin usually disappears when the patient lies down, and appears when he is in the erect position though to a lesser extent when he is moving about. Standing in the position of attention, especially with heels, buttocks, shoulders and head against a vertical surface such as a wall, increases the albuminuria, on the other hand, if while he is standing the patient places one foot on a stool or chair, the albuminuria disappears.

All of the positions which produce albuminuria also produce a lordosis whereas the "nonalbuminous" positions tend to correct this posture. The production of albuminuria has been explained as due to the pressure of the lumbar vertebrae indirectly on the left renal vein with consequent interference with circulation of a "passive congestion" type. By catheterizing the ureters of patients with this condition Sonne has shown in a small series of cases that when albuminuria was present, it always came from the left ureter and never from the right thus lending support to this theory.

Diagnosis depends upon finding specimens of urine free from albumin. The urine should be passed before rising from bed in the morning, as well as later in the morning. The absence of albumin in the first and presence in the second is diagnostic. If the specimens of the two hour renal function test be examined for albumin it may be found in some and not in others. Occasionally it may be necessary to have the patient empty his bladder and then lie down in a 'curled up' posture for an hour or two, voiding at the end of each hour, to obtain an albumin free urine. In all cases renal function tests should be carried out. They must fall within normal limits to permit of the diagnosis of orthostatic albuminuria. The condition occurs more commonly in hyposthenic individuals though it may appear in the robust. Casts are present not infrequently.

No treatment is necessary though exercise to counteract the lordotic tendency may aid in eliminating the condition. The albuminuria *per se* is not of importance. Parents should be reassured as to the innocent nature of the condition. It may persist for years but usually disappears with the period of adolescence.

sacrificed are ones such as the skin and skeletal muscles to be followed by the kidneys and liver and finally the central nervous system, lungs and myocardium.

This diversion of the reduced blood volume to parts where it is most essential is apparently accomplished through selective vasoconstriction. The skin and the skeletal muscles would be the first to show evidence of such being the case. These tissues can endure profound ischemia and reveal few after effects with eventual complete restoration of function. The kidneys, however, cannot stand such a degree of ischemia and will early show a deficiency of function which may be permanent leading to fatal uremia or it may be reversible depending upon the degree and duration of the ischemia. It would seem obvious that there is a deep purpose for the blood supply to the lungs, myocardium and central nervous system to be maintained as long as possible against all hazards. The failure of function of any one of them would lead to early death.

It would be impossible to deal with all the various causes of shock as there have now been enumerated somewhat over thirty but we shall take as examples acute loss of whole blood as in hemorrhage, plasma loss as in burns and cholera or the simpler dehydration of water and electrolyte loss as in persistent vomiting in all of which there is eventually a grave fall in blood pressure.

The first effect on the kidney would be vasoconstriction leading to decreased renal blood flow with a parallel reduction of secretion or oliguria even to anuria. In this phase the general blood pressure may for a time be maintained which is part of a defense reaction but this may in a short time also fall. There is then a summation of causes leading to renal ischemia. If these are not too complete or prolonged and the general circulation is restored renal function will be resumed without permanent damage to the kidney cells. It must be appreciated that renal vasoconstriction alone without a low blood pressure may cause a degree of renal failure and if sufficiently prolonged may lead to irreversible renal damage.

The brilliant experiments of Tinetti and collaborators would indicate that there may be another manner by which renal failure and uremia may be produced after injury. They demonstrated that the application of a tourniquet to the left hind leg of a rabbit for some hours caused a withdrawal of blood from the left renal cortex and a great acceleration of blood flow through the medulla. This is revealed by the increase of the total blood flow through the kidney the venous blood being almost arterial in color and the renal vein being distended and pulsating. It was suggested by Tinetti that the blood flow through the cortex was shunted through the medulla thus preventing its filtration in the cortex leading to a cessation of renal function. This phenomenon was apparently of neurogenic origin and not comparable to the conditions arising in hemorrhage or traumatic shock. In the latter the renal blood flow is not accelerated but greatly diminished and the kidney continues to extract 8, to 90 per cent of para amino hippuric acid from the plasma indicating that such blood as continued to perfuse the kidneys was reaching nephrons of normal excretory capacity.

### Renal Arteriosclerosis

Up to recent times there was considered to exist a close relation between arteriosclerosis and renal failure. This apparently arose from a confusion of the anatomical lesions resulting from the arteriolar sclerosis of hypertension (primary contracted kidney, page 450), secondary arteriolar changes occurring in the terminal stages of chronic hemorrhagic Bright's disease (secondary contracted kidney see page 1266), and true arteriosclerosis of the later decades. It is the last group which are at present being considered. The renal arteries usually reveal considerable atheroma and there may be definite infarcts with cystic formation and a general atrophy of the cortex. The effect upon renal function is not at all distinctive and here again it is surprising the small amount of functional disability which may result. In fact the arteriosclerotic kidney cannot be accused of producing any definite clinical pattern. It is true that hematuria may be intermittent, that proteinuria and cylindruria may be found but, serious interference with renal function as represented by nonprotein nitrogen retention etc. is seldom conspicuous, and uremia is rare.

### Infarcts of the Kidney

These fall into three main groups, small embolic infarcts, arteriosclerotic infarcts and the massive infarction of bilateral necrosis (lower nephron nephrosis).

Emboli may lodge in the kidney in the course of any septicemic process, if they be relatively large they are accompanied by the usual symptoms of sudden pain (in the loin) shock of varying degree, oliguria and hematuria. These symptoms usually subside in the course of a few days but the episodes may be repeated.

In focal glomerulonephritis the infarcts are small, and involve only a small portion of individual glomeruli. The only symptom may be the presence of hematuria, gross or microscopic. They are common in the course of subacute bacterial endocarditis. Total renal function usually remains unimpaired, and the treatment is that of the general disease, although sometimes the renal lesion is so extensive as to lead to uremia.

### Lower Nephron Nephrosis

#### Tubovascular Renal Syndrome

Grave impairment of renal function even leading to fatal uremia has been described following shock due to severe trauma or hemorrhage, crushing injuries, posttransfusion reactions, toxic effects of sulfonamides, arsenic, mercury, carbon tetrachloride and other nephrotoxins as will be pointed out below. The renal ischemia which may be of a severe degree in shock causes pronounced tissue anoxia which acts in the role of a nephrotoxin.

All tissues are not equally affected by anoxia for example the skin and voluntary muscles appear to stand long periods of ischemia while the central nervous system and the myocardium are particularly sensitive and the liver and kidney stand somewhere midway. There is ample evidence to suggest that as the circulating blood volume is reduced the first tissues to be



and inorganic phosphorus. Vomiting may be present, and even severe but there are usually none of the classical symptoms of uremia. What urine is secreted is of low specific gravity, contains protein and some blood cells and in the early stages heme pigment or heme stained casts may be found. There is no definite pattern to the blood pressure levels which are essentially low but may rise moderately. The oliguria has been reported as lasting as long as nineteen days but unless the urinary secretion is restored early death occurs on the average on about the eighth day.

*Treatment* consists in measures to combat the shock at the onset to restore the circulating blood volume with blood plasma or salt solutions as indicated and to raise the blood pressure level. In those cases which follow the transfusion of incompatible blood the prompt administration of sufficient alkalis to produce an alkaline reaction in the urine has been thought to be of value. Continuous oxygen therapy should be given in high concentration in order to raise the amount in physical solution in the plasma and so help to reduce the tissue anoxia. The use of peritoneal lavage or the artificial kidney if available is strongly indicated as it must be appreciated that the lesions in many of these cases of lower nephron nephrosis are reversible.

**Crush Syndrome**—In addition to the nephrotoxic effect of moribund there may be additional factors present. In this regard the crush syndrome must be mentioned. Although scattered references to this condition are found in the literature before 1940 it was as the result of the mass bombing of civilian centers when cases could be followed from the initial injury to the terminal stages some days later that attention was focused upon an old syndrome with a new title.

The name was derived from crushing injuries of soft parts with or without fractures. The victim when released was in shock or shortly developed it and it might be fatal or he might recover from this phase and pass into a stage of progressive urinia with hypertension. But in these cases there are two features of particular significance namely (1) In the early stages there is an excessive amount of potassium in the urine. This is supposed to be derived from the macerated muscle of the crush injury. (2) Although in all forms of uremia there may be an increase of the blood potassium in this syndrome with the onset of oliguria the blood potassium continues to rise at an excessive rate until it may reach a level of 30 to 40 mg per cent. Myoglobinuria with obstructive casts was supposed by some to play an important role in the renal lesions but now the consensus is that the detritus may only contribute to the progress of the lesions initiated by the ischemia of the initial shock. It has been suggested that the phenomenon described by Trueta and mentioned above may account for some cases of renal failure in this syndrome. But it would seem necessary in such cases for the crushing injury to involve both limbs and to have the same effect as a bilateral tourniquet.

It is postulated that the progressive and excessive increase in blood potassium is due to its reabsorption from the tubules in excessive amounts derived from the macerated muscle. Death is considered to be due to a combination of uremia and cardiac failure caused by potassium intoxication.

This first or ischemic phase may be followed if the shock continues by a second stage where if there is any urine passed, it is of low specific gravity with low urea clearance. This would indicate renal damage. But the degree cannot be assessed accurately. The renal recovery may lag behind the shock and eventually be complete indicating that the anatomical lesion has been reversible. On the other hand after the shock has been recovered from kidney function may improve for a while and then fail again indicating progression of the lesion. Finally there are those cases where renal failure is progressive indicating permanent and irreversible injury leading to uremia and death.

It is difficult to foretell which of these three results may occur. The margin of safety is narrow and many patients in severe shock may die before uremia develops. On the other hand it is impossible to say which patients would recover if the uremia could be controlled by an artificial kidney or peritoneal lavage in the hope of eventual reversibility.

The character of the renal lesions has been extensively studied by Lucke and Mallory in man after battle injuries by Bidenach and Darmady in rabbits and by Van Slyke in dogs. Although there are some differences as to details in general the findings may be summarized as follows: glomeruli and proximal tubules practically undamaged; distal convoluted tubules and thick tubules of Henle degenerated and showing necrosis. Mallory points out that in the first 24 hours visible lesions do not appear which would indicate that the lesions are aftereffects of damage not histologically demonstrable suffered by the tubular cells during the period of shock.

In Lucke's series of 538 cases 403 were subjects of the type of shock mentioned above while 67 cases were due to poisoning caused by substances such as sulfonamides, arsenic, carbon tetrachloride, etc. Therefore it would appear that nephrotoxic agents as well as shock produce the same type of lesion. He coined the term 'lower nephron nephrosis' to cover all these conditions.

Lucke pointed to the similarity of the findings in shock to those noted by Richards when he studied the effect of nephrotoxic substances such as mercuric chloride on the nephron of frogs. This was in brief that the glomerular filtration took place at a normal rate but the entire filtrate was reabsorbed from the tubules. In other words the cells of the tubules have lost their normal capacity of selective reabsorption by which they take back from the glomerular filtrate sufficient water to prevent dehydration, glucose, amino acids, electrolytes, etc. and discard or in the return of urea, uric acid, creatinine, etc. and excess water and electrolytes. In Richards' nephrotoxic kidneys the tubules act as a dead membrane and everything passes through and there is anuria.

It is true that this process has not been definitely demonstrated in the shock kidney as in Richards' nephrotoxic frogs but it has been shown by experiments in dogs that such kidneys lose most or all of their power to extract para amino hippurate from the renal plasma nor can they concentrate the glomerular filtrate both of which facts would point to a tubular damage.

The clinical features include pronounced oliguria or complete anuria rapidly increasing retention of nonprotein nitrogen, creatinine, potassium

that in cases of infection of the lower urinary tract the infection reaches the kidney by passage through the lymphatics into the blood stream. In the lesions of the pelvis, contributing factors are stasis and mechanical injury, as from obstruction and "back pressure"

**Symptoms**—Certain symptoms and signs are common to all of these infections as they have their origins in the same physiologicopathological processes. Pain is due to stretching of the renal capsule or pelvis. It is felt in the "back" more definitely in the loin. If tenderness be present, it is most acute in the costolumbar angle, though if the kidney be palpable through the anterior abdominal wall it also will be tender. Frequency is also dependent reflexly upon irritation of the renal pelvis or the ureter, the micturition may be painful, though if this be a marked symptom disease of the bladder should be suspected. Fever is of the type which might be expected in a pyogenic condition where the amount of absorption of septic material is related to the degree of drainage. There may be an initial chill often followed by others, the fever may be mild or intense, and of the intermittent or remittent type when there is some drainage, continuous where drainage is absent. The leucocyte count also will vary with the degree of toxicity and absorption. Nausea and vomiting are other systemic symptoms which are related to the degree of general depression of the patient; they may be absent. Albuminuria of the "febrile" type will be found, but unless the suppurative process takes place in a portion of the kidney communicating with the renal pelvis no pus will be present in the urine. In some cases blockage of the ureter below the pelvis will effectually prevent the passage of the pus where pus is present red blood cells are usually found also in microscopic amounts. If the inflammatory lesion has been of such a nature as to involve a large amount of the renal parenchyma, there may be a loss of renal function of varying degree with associated signs and symptoms as outlined above.

**Cortical abscess** is most frequently found in association with an existing or preceding furuncle or carbuncle or other staphylococcus infection of the skin or other tissues. Symptoms may be vague and merely those of a general infection. At times loin pain may be severe but pyuria is rarely a feature *owing to the situation of the inflammatory process in a portion of the kidney away from communication with the pelvis*. The infection may spread through the capsule of the kidney into the perinephric tissue forming a perinephric abscess when general symptoms of sepsis will become more severe followed by local edema of the skin over the costolumbar region and swelling in this region.

In general septicemia multiple abscesses of the kidney may occur in many cases symptoms and signs are lacking and the lesion is found only at autopsy.

**Pyelitis**—Pyelitis should more properly be called pyelonephritis as the inflammatory process also involves the parenchyma of the kidney to a greater or lesser extent. Apart from the infecting organism which is usually the colon (or tubercle) bacillus the chief contributory factor is obstruction to the free drainage of the kidney pelvis as from "kinking" of the ureter in ptosis of

A rational feature in the treatment, in addition to the prevention and reversal of shock and the control of the uremia by the artificial kidney or peritoneal lavage would be to combat the potassium intoxication. This may be attained through a proper balance of the fluid used in peritoneal lavage or by the administration intravenously of calcium which is an antagonist of potassium. Insulin and glucose have also been advocated.

**Hepatorenal Syndrome**—It has long been appreciated that renal failure may supervene in chronic liver disease and it may also be associated with acute liver lesions such as acute hepatitis or after hepatotoxins like chloroform, cinchophen, dioxane and carbon tetrachloride. It has also been suggested that this may be a prerenal uremia. There are, however, cases reported following shock from hemorrhage and burns and more rarely after dehydration due to simple water and electrolyte loss.

It has been mentioned above that all organs are not equally affected by the vasoconstriction in shock. The liver may follow after the kidney and so hepatic lesions may be less common than the renal. On the other hand jaundice is a more obvious sign than is early oliguria. In cases after severe postpartum hemorrhage with shock it may be shown that incipient signs of renal failure such as rising NPN, lowered  $\text{CO}_2$  combining power and oliguria with low specific gravity may precede the jaundice. This hepatorenal combination is a particularly dangerous one as the detoxicating power of the liver as well as other important functions are impaired, and this combined with the failure of renal excretion of toxins permits the rapid accumulation of those noxious but unknown substances which make the final stages of hepatic and renal failure so much alike.

The treatment of the hepatorenal syndrome is most unsatisfactory. It is obvious that the ischemia of shock should be combated by all means. It would also seem indicated that the diet should be high in carbohydrate and low in fat. The place of protein is still disputed. It is a protector of the fatty liver but it may be possible that it is the source of toxic end products which the liver normally detoxifies. The use of methionine in 2 Gm (30 grains) doses four times daily has its advocates, vitamin B complex intramuscularly is also recommended while the therapeutic role of choline is still doubtful.

### Infections of the Kidneys

These include those diffuse and focal inflammations of the kidney parenchyma and pelvis in which we are able to demonstrate a definite bacterial etiology.

**Etiology**—The bacteria concerned fall into three main types. 1 The colon group found almost exclusively in infections of the pelvis, rarely where the parenchyma has been the original focus. 2 The pyogenic cocci (staphylococcus, streptococcus, pneumococcus) which affect the parenchyma of the kidney primarily. 3 The tubercle bacillus giving rise to lesions which involve both parenchyma and pelvis and the lower urinary tract.

Bacteria reach the kidney through the blood stream or the lymphatics or by retrograde infection of the ureter in cases where the latter has been injured as by obstruction. The work of Wallace however tends to show

that in cases of infection of the lower urinary tract the infection reaches the kidney by passage through the lymphatics into the blood stream. In the lesions of the pelvis, contributing factors are stasis and mechanical injury, as from obstruction and "back pressure."

**Symptoms**—Certain symptoms and signs are common to all of these infections as they have their origins in the same physiologico pathological processes. Pain is due to stretching of the renal capsule or pelvis, it is felt in the back, more definitely in the loin. If tenderness be present it is most acute in the costolumbar angle, though if the kidney be palpable through the anterior abdominal wall it also will be tender. Frequency is also dependent reflexly upon irritation of the renal pelvis or the ureter. The micturition may be painful though if this be a marked symptom disease of the bladder should be suspected. Fever is of the type which might be expected in a pyogenic condition where the amount of absorption of septic material is related to the degree of drainage. There may be an initial chill often followed by others. The fever may be mild or intense and of the intermittent or remittent type when there is some drainage continuous where drainage is absent. The leucocyte count also will vary with the degree of toxicity and absorption. Nausea and vomiting are other systemic symptoms which are related to the degree of general depression of the patient they may be absent. Albuminuria of the "febrile" type will be found but unless the suppurative process takes place in a portion of the kidney communicating with the renal pelvis no pus will be present in the urine. In some cases blockage of the ureter below the pelvis will effectually prevent the passage of the pus where pus is present, red blood cells are usually found also in microscopic amounts. If the inflammatory lesion has been of such a nature as to involve a large amount of the renal parenchyma there may be a loss of renal function of varying degree with associated signs and symptoms as outlined above.

**Cortical abscess** is most frequently found in association with an existing or preceding furuncle or carbuncle or other staphylococcus infection of the skin or other tissues. Symptoms may be vague and merely those of a general infection. At times loin pain may be severe but pyuria is rarely a feature owing to the situation of the inflammatory process in a portion of the kidney away from communication with the pelvis. The infection may spread through the capsule of the kidney into the perinephric tissue forming a perinephric abscess when general symptoms of sepsis will become more severe, followed by local edema of the skin over the costolumbar region and swelling in this region.

In general septicemia multiple abscesses of the kidney may occur in many cases symptoms and signs are lacking, and the lesion is found only at autopsy.

**Pyelitis**—Pyelitis should more properly be called pyelonephritis as the inflammatory process also involves the parenchyma of the kidney to a greater or lesser extent. Apart from the infecting organism which is usually the colon (or tubercle) bacillus the chief contributory factor is obstruction to the free drainage of the kidney pelvis as from "kinking" of the ureter in ptosis of

the kidney, or blockage of the ureter from calculi or external pressure. The frequency of right sided pyelitis during pregnancy is ascribed to pressure by the enlarged rotated uterus upon the right ureter.

*Symptoms and signs* vary according to the severity of the infection and the degree of damage possible. An initial chill is frequent, and recurrences are also frequent. The fever varies in degree, and is accompanied by a rapid pulse. The patient may appear quite septic, and delirium may be a prominent symptom. Pain and tenderness in the loins is common, not infrequently it may be bilateral, one kidney or both may be palpable. Urinary symptoms may be severe and the urine literally 'loaded with pus' so as to be visible macroscopically, the reaction is acid to litmus paper and the urinary volume may be reduced. In severe cases it is not unusual to find fine crepitations at the base of the lung on the side of the involved kidney, they clear up with the subsidence of the renal infection.

The *prognosis* for acute attacks of pyelitis is good though they may be prolonged and frequently may pass into the chronic state in which acute exacerbations are not infrequent. If the lesion has been sufficiently destructive of the renal parenchyma, hypertension and other signs of renal failure may supervene.

**Tuberculosis of the Kidney**—No attempt will be made to discuss this condition in detail for a fuller description the reader is referred to any standard textbook of urology.

As a general rule renal tuberculosis is unilateral in situation except in advanced cases. The primary lesion is in a papilla whence it spreads until ultimately it breaks through into the renal pelvis, giving rise to symptoms. The process of spread in the kidney follows the same general rules as in other organs.

Tuberculous infection of the pelvis gives rise to the same local symptoms as do other infections the most prominent being pain, frequency of urination, and hematuria. The frequency is more prominent at night, dysuria may be quite distressing, becoming even more severe when the bladder is ultimately involved. Hematuria is usually mild but pus is always present. There may be a dull pain in the loins occasionally there is actual renal colic. Systemic symptoms may be absent or very mild unless the disease be far advanced. Careful examination will frequently demonstrate a tuberculous focus in the lungs.

*Diagnosis* depends finally upon the demonstration of tubercle bacilli in the urine. Pielography will usually reveal evidences of disease in the pelvis and urine collected by ureteral catheter will contain pus and have the low urea content of impaired renal function.

**Syphilis**—Syphilitic infection of the kidney usually occurs during the secondary stages of the disease and in its clinical and pathological features resembles the "pure nephrotic state discussed above under Bright's disease. Under present day conditions it is rare to see the massive edema albuminuria may be the outstanding feature that attracts attention to the condition. If the patient has been receiving mercury the renal lesion might be ascribed to

toxic effects of this drug, but mercury will never produce the metabolic changes seen in the nephrotic state.

The prognosis is good as the condition usually clears under treatment of the syphilis.

**Treatment of Renal Infections**—Cortical abscess requires antibiotics or chemotherapy. If signs of perinephric abscess develop surgical drainage is indicated. No local treatment is useful for the multiple abscesses of septicaemia but all measures should be directed to the treatment of the general condition.

The discovery of the sulfonamides and the various antibiotics has made the successful treatment of pyelitis much easier and shorter in duration. In many cases the exhibition of 1 gram (15 grains) of a sulfonamide (such as sulfadiazine) three times daily will be sufficient to bring the condition under control in a few days. If the infecting organism be one of those that are susceptible to penicillin the intramuscular injection of this drug in dosage sufficient to keep up a good concentration in the urine will likewise have a rapid effect. The majority of the organisms associated with this condition are gram negative and not susceptible to penicillin but good results can be obtained by using streptomycin in divided doses of 1 to 2 grams daily intramuscularly (see Chapter XXI).

The main principle in the treatment of pyelitis is to establish drainage which is best achieved by posturing the patient in such a position as will aid in relieving kinks in the ureter; in general this implies lying flat on the back without head pillows but a small roll inserted under the lumbar curvature. In some cases as in pyelitis of pregnancy it may be necessary to raise the foot of the bed to relieve the pressure of the uterus on the ureter. At the same time flushing out from above should be promoted by the forcing of fluids. Where there is no vomiting the total intake by mouth should reach a maximum of three to six liters daily for an adult as water may prove unpalatable fruit juices and 'imperial drink' may be used freely. If vomiting interferes with the fluid intake it may be necessary to administer fluids by rectum intravenously and subcutaneously.

Mandelic acid can be given in the form of ammonium mandelate of which approximately gr. xxx (2 g.) should be given by mouth four times daily. It is essential that the pH of the urine should be kept below 5.3; if it be higher than this it will be necessary to administer ammonium chloride as well in sufficient dosage to produce the desired degree of urinary acidity.

In certain cases cystoscopy with catheterization of the ureters may be necessary to relieve obstruction and overcome stasis. Occasionally the renal pelvis is washed out with dilute antiseptic solutions.

The treatment of tuberculosis of the kidney in the majority of cases is surgical involving excision of the affected organ. If the disease is bilateral or if there be extensive disease elsewhere, treatment may have to be symptomatic only.

*Syphilis of the kidney* usually responds well to treatment which is preferably with bismuth at the beginning followed by arsenicals and mercury later.

In this condition the apparently paradoxical situation arises of using the metals which may injure the kidney to treat a condition characterized by massive albuminuria. Penicillin has overcome this impasse.

### Nephrolithiasis (Renal Calculus)

In this condition solid foreign bodies known as "stones" are found in the calyces or pelvis of the kidney, which may give rise to symptoms, or be relatively asymptomatic.

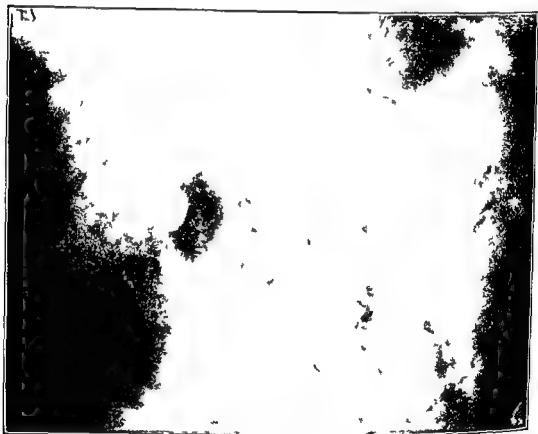


Fig 461—X ray showing a single calculus in the pelvis of the right kidney

The chief factors in the formation of renal calculi are perversions of metabolic processes, infection and stasis in the urinary tract. Various theories have been advanced to explain the mechanism of stone formation, one school holding that there is a central nucleus of colloids (often of infective origin) on which the crystalloids are precipitated, the other that the crystalloids are deposited from the urine in which they are present in concentrated solution. In the latter case precipitation follows the physical laws of solution, in which salt and hydrogen ion concentration are important factors. In all cases stasis and a concentrated urine appear to be the chief physiological factors, while infection may play a further part in the process. Vitamin A deficiency (see page 784) has also been accused of being responsible for nephrolithiasis through



the resultant keratinization of the epithelial lining of the renal pelvis and the ureter. Sulfonamides are today a relatively frequent cause.

In general calculi may be classified according to their chemical composition the principal types including calcium uric acid, phosphate, oxalate and rarely cystin. Recent studies have served to emphasize that calcium stones may be the outstanding indication of hyperparathyroidism, in which the urinary excretion of calcium is greatly increased, in these cases estimation of the level of calcium and phosphorus in the serum may be of great importance in determining the etiology. Similarly in the individual with a gouty diathesis study of the uric acid in blood and urine may yield significant evidence.



Fig. 46.—X-ray showing staghorn calculus in the pelvis of the left kidney.

Phosphate stones are more usual in cases with stasis and infection, oxalate stones are usually combined with calcium to form the relatively insoluble calcium oxalate. Stones several generations ago were usually found in children (vitamin A deficiency?) while now they may appear at any age period but are more common in the third and fourth decades and in men than in women.

**Symptoms**—The best known and most easily recognized symptom is renal colic. A typical attack begins with severe pain in the loin or back radiating around to the front of the abdomen and down to the external genitalia or the inner side of the thigh. The radiation corresponds to the region involved loin pain from the renal pelvis abdominal and genital from the ureter according to the level. The pain is extremely acute colicky in nature and is usually

associated with varying degrees of shock, which may produce cold sweat, vomiting, and general collapse. Frequent and painful urination is a prominent symptom caused by reflexes from irritation of the pelvis and ureter. The urine contains blood in gross or microscopic amounts, a few pus cells may also be present. Generally the old rule holds true, "the smaller the stone the greater the colic" a "crystal" may cause severe colic and yet be too small to cast a recognizable x ray shadow. This type is frequently spoken of popularly as "gravel." The colic usually lasts until the stone passes down into the bladder or slips back into the pelvis, when the relief is great, and the exhausted patient usually sinks into sleep.



FIG 463—X ray showing a small calculus in the left ureter

Where stasis is marked and infection is present symptoms may be vague or consist merely of pain in the back or "lumbago." In these cases large calculi may be deposited in the pelvis and calyces forming the typical stag horn calculus. Frequently symptoms may be absent and the calculi are found by x ray in the course of investigation of the renal tract or vertebrae.

The sequelae of calculi depend upon the anatomicophysiological changes produced. As a rule small calculi cause no lasting ill effects, and are usually passed in the urine. Larger stones may become impacted in the ureter when they may ulcerate through or more commonly give rise to atrophy of the kidney or hydronephrosis as discussed below. In the rare instance where there is bilateral impaction of stones, anuria will result, with death if the con-

dition is not relieved. In these cases there is rapidly increasing nitrogen retention in the blood, but no changes in the ocular fundi, nor is there necessarily hypertension. Uremic symptoms may not occur or they may appear only as a terminal event.

**Diagnosis** —Where there is a typical colic and hematuria, the diagnosis is easy. As stated above x ray examination may give negative results in the presence of a small stone. In less typical cases ultimate diagnosis may rest upon x ray and cystoscopic examination. In some instances the x ray shadow of a phlebolith has appeared to be typical of a calculus until cystoscopy and ureteral catheterization showed that the shadow did not correspond with the position of the ureter.

Acute appendicitis and gallstone colic may occasionally offer difficulties in the differential diagnosis of a right renal calculus.

**Treatment** —Acute colic will require large doses of sedatives. As a rule a quarter gram of morphia by hypodermic injection will be quite ineffectual in the average adult, it is better to give a half grain at once and repeat sixth or quarter grains according to the indications. If the pain refuses to yield it may be necessary to give whiffs of chloroform though it should be borne in mind that this measure is not without danger. After the pain has been relieved the patient should be kept warm and allowed rest. Fluids should be forced to "flush out" the urinary tract by increased secretion. Frequently morphia will relieve the spasm of the ureter sufficiently to allow the calculus to pass to the bladder and so out the urethra. Frequently the stone can be recovered when passed, though if it be small it may be missed unless all the urine be strained through cheesecloth when the calculus is left visible. In more chronic cases treatment becomes a surgical problem.

Following the passage of a stone there may be formation of others. In some cases this can be prevented by increasing the fluid intake with the purpose of keeping the urine dilute. If there be a gouty diathesis appropriate treatment for this condition should be instituted. In cases due to hyperparathyroidism surgical removal of the hyperfunctioning glandular tissue is indicated.

### Hydronephrosis

Hydronephrosis is the term applied to that condition in which there is dilatation of the renal pelvis with pressure on and subsequent atrophy of the renal parenchyma. It is induced by any condition which interferes with drainage of the urine once it has been secreted by the kidney, such as stricture of the urethra, prostatic hypertrophy, impacted ureteral calculus, kinking of the ureter, external pressure on the ureter as from neoplasms, etc. Where obstruction is complete there is usually a small degree of dilatation of the tract above the site of obstruction followed rapidly by atrophy of disuse of the renal tissue. It is in incomplete obstruction such as the intermittent type that dilatation proceeds to the greatest extent. Sooner or later infection enters the stagnant urine and inflammatory changes take place. Ultimately only a shell of kidney substance is left in which there is little or no function.

enclosing a collection of infected urine or pus. This final condition is differentiated as "*pyonephrosis*."

In the early stages the symptoms are those referable to dilatation and stretching of the pelvis and capsule, later those of the septic state, and of failing renal function become more prominent. Thus there is dull aching pain in the loin or abdomen, frequency, pyuria, fever and a general septic state as the condition progresses. Cystoscopy with pyelography and estimation of the renal function by dye excretion and urea content of the urine collected by ureteral catheter will furnish evidence of the degree of involvement.

"Dietl's crises" are acute intermittent occlusions of the renal pedicle due to torsion when the poles of a freely movable and displaced kidney assume an anteroposterior position. There is acute pain in the loin, chills, pyrexia, sweating, leucocytosis, and often collapse. There is also some hematuria and oliguria, although there is frequency of desire. A tumor is palpable in the loin which usually disappears on manipulation by returning the kidney to its normal position.

Prognosis depends on the degree of interference with drainage, and the possibility of restoring free drainage by relieving the cause of obstruction. Treatment is thus usually surgical in nature, and may involve nephrectomy.

### TUMORS OF THE KIDNEY

Clinically these fall into two main groups, those of childhood occurring from birth to about five years, and those of later life from forty years on. These groups correspond in general pathologically with the embryomata and sarcomata, and the carcinomata (including the hypernephromata) respectively. In generalized carcinomatosis, metastases may appear in the kidney often bilaterally, the primary tumors, however, are practically always unilateral. Benign tumors of the kidney are not frequent and are rarely diagnosed clinically.

Of the signs and symptoms the earliest and most important is hematuria which is usually spontaneous and may be quite profuse, often there are repeated attacks. It is painless unless clots be formed which in their passage to the bladder may give rise to ureteral colic. Pus is not usually found in the urine.

The tumor mass may not be palpable early in the disease process, but later it can be felt in the loin or through the abdominal wall, it usually moves with respiration.

A sign which has been stressed is the presence of a varicocele which does not disappear when the patient lies down due to pressure of the tumor mass on the spermatic vein of that side. Pain in the loin may be present as a dull ache, it is ascribed to stretching of the kidney capsule. Renal function is usually relatively little impaired throughout the course and death takes place from the cachexia associated with malignant growths. Metastases in the lungs are not infrequent.

Diagnosis—In the early stages the hematuria may be suggestive of renal calculus or tuberculosis, in the later stages the mass may be confused with

congenital cystic kidney or pyonephrosis Cystoscopic examination and pyelography with x ray may be of aid in making a differential diagnosis

**Treatment**—Treatment is surgical, in some cases it may be possible to remove the growth completely, but usually this is impossible when treatment will be purely palliative

### References

- Addis, T Renal Function and the Amount of Functioning Tissue. The Ratio Urea in One Hour's Urine  
Urea in 100 cc Blood After Giving Urea and Water Arch Int. Med. 30  
378 1920
- Addis T A Clinical Classification of Bright's Disease, J A M A 85 163, 1925
- Albright F Baird P C, Cope O, and Bloomberg E Studies on the Physiology of the Parathyroid Glands IV Renal Complications of Hyperparathyroidism, Am J M Sc 187 49 1934
- Albright F Sulikowitch H W and Chute R Nonsurgical Aspects of the Kidney Stone Problem J A M A 113 1049 1930
- Badenoch W W and Darmady, E W The Effects of Temporary Occlusion of the Renal Artery in Rabbits and Its Relation to Traumatic Uræmia J Path & Bact 59 19 1944
- Berglund H, Medes G, Huber G C, Longcope, W T and Richards A. N The Kidney in Health and Disease Philadelphia 1930 Lea & Febiger
- Blackfan K. D Acute Nephritis in Children With Special Reference to the Treatment of Uræmia Bull Johns Hopkins Hosp 39 69 19 6
- Bywaters E G J Ischemic Muscle Necrosis Following Crushing Injury Traumatic Edema Crush Syndrome Traumatic Anuria Compression Syndrome Type of Injury Seen in Air Raid Casualties Following Burial Beneath Debris J A M A 124 1103 1109 1944
- Bywaters E G L and Dible J H Renal Lesion in Traumatic Anuria J Path. & Bact 54 111 10 1944
- Cushny A H The Secretion of the Urine, London 1911 Longmans Green & Co
- Duff G L and More R H Bilateral Cortical Necrosis of the Kidneys Am J M Sc 201 4 9 1941
- Epstein A A Thyroid Therapy and Thyroid Tolerance in Chronic Nephrosis, J A M A. 87 913 1926
- Fishberg A M Hypertension and Nephritis Philadelphia 1939 Lea & Febiger
- Hartman F W, Bollinger A. and Doub H P Functional Studies Throughout the Course of Poentgen Ray Nephritis in Dogs J A M A 88 139 1927
- Kempner Walter Treatment of Kidney Disease and Hypertensive Vascular Disease With Rice Diet III North Carolina M J 11 1 1945
- Kimmelstiel I and Wilson C Intracapillary Lesions in the Glomeruli of the Kidney Am J Path 12 83 1946
- Kolff W J New Ways of Treating Uræmia London 1947 J & A Churchill Ltd
- Letter L Nephrosis Medicine 10 130 1931
- Lucké Ballin Lower Nephron Nephrosis Mil Surgeon 99 341 1946
- MacKenzie H W and Wallace A B The Lymphatics of the Lower Urinary and Genital Tracts. An Experimental Study With Special Reference to Renal Infections Tr Am A Genito Urinary Surgeons 28 345 1935
- MacLean H Modern Methods in Diagnosis and Treatment of Renal Disease Philadelphia 1924 Lea & Febiger
- Mallory T H Hemoglobinuric Nephrosis in Traumatic Shock Am J Clin Path 17 40 1944
- Mosenthal H O Renal Function as Measured by the Elimination of Fluids Salt and Nitrogen and the Specific Gravity of the Urine Arch Int. Med 16 733 1910

- Murray G. Heparin in Thrombosis and Blood Vessel Surgery *Surg Gynec & Obst* 2340, 1941
- Richards, A. N. *Methods and Results of Direct Investigations of the Function of the Kidney*, Baltimore, 1932, Williams & Wilkins Co
- Rowntree, L. G., and Geraghty, J. T. An Experimental and Clinical Study of Phenol sulphophthalein in Relation to Renal Function in Health and Disease *J A M A* 284 1912
- Schemm, F. R. High Fluid Intake in Management of Edema, Especially Cardiac Edema *Ann Int Med* 17 9, 2 1942
- Smadel, Jos E., and Leo E. *J Exper Med* 65 527, 541, 557, 1937
- Sonne, C. Beitrag zur Aetiologie der lordotischen (orthostatischen) Albuminurie, *Ztschr f klin Med* 90 1 1920
- Frueta, I. Barclay A. I. Daniel P. and Franklin K. J. Renal Pathology in the Light of Recent Neurovascular Studies *Lancet* 251 237, 1940
- Van Slyke, D. D., McIntosh, J. F., Møller F., Hannon, R. R., and Johnston, C. Studies of Urea Excretion. VI Comparison of the Blood Urea Clearance With Certain Other Measures of Renal Function, *J Clin Investigation* 8 357, 1930
- Volhard F. and Fahr T. *Die hrichte Nierenkrankheit*, Berlin, 1914 Julius Springer

## CHAPTER XIX

### INFECTIOUS DISEASES

In the preceding chapters some infectious diseases have been described because of the fact that their principal clinical manifestations warranted their being considered as diseases under a special system rather than under their etiological cause, which is the customary method. This latter does not seem to have any particular virtue as it dissociates the infection from the clinical picture of its first manifestations which is the important period for its recognition if specific treatment is to be most efficacious.

The diseases now to be considered arranged according to their etiology are the following:

<i>Bacillary</i>	<i>Syprochetal</i>	<i>Virus Diseases</i>
Leprosy	Syphilis	Smallpox
Tetanus	Yaws	Varicella
Tulariaemia	Latente fever	Herpes zoster
Anthrax	Felting fever	Rabies
Glanders		Dengue
Illague	Coccal	Epidemic pleurodynia
<i>Bacterial</i>	Staphylococcal septicaemia	Paratyphoid
Typhus fever	Streptococcal septicaemia	Lymphogranuloma inguinale
Typhoid fever	Dysentery	Foot and mouth disease
Rocky Mountain fever	Gonorrhea	Swine fever
Trench fever		
Carrion disease	Protozoal	Nematode
Q fever	Leishmaniasis	Filaria
Bull's fever	Trypanosomiasis	
Bubonic plague	Malaria	
	Toxoplasmosis	

But this classification does not give information as to the manner in which the patient is infected. Furthermore it is important to appreciate that certain diseases may be recognized by a characteristic primary lesion at the portal of entry of the infecting agent, and an early diagnosis can thereby be made. In others it may not be particularly specific or may be so minute as to pass unnoticed by the patient or the physician. The agent when inoculated may enter the blood stream directly and so be disseminated. Again it may pass along the lymphatic channels and be temporarily or permanently arrested by the regional lymph glands or first line defense from where it may eventually be disseminated via the blood stream to all the tissues. These may not all be equally affected and the secondary lesions may vary considerably in different tissues. This is probably determined by their power of defense or lack of defense. Occasionally the virus travels along special tissues as the nerves in rabies, and as a consequence the entire localization in this disease is within the nervous system. The majority of these diseases gain access through the skin either on account of abrasions, punctured wounds or bites of various animals or insects. In some diseases the means of transmission and inoculation often shed light upon the possible diagnosis. There is an important group that is inoculated directly through the skin or mucous membrane and the place where this occurs

can be fairly definitely located in most instances. There is not necessarily any detectable break in the continuity of the skin but a minute injury undoubtedly is present to allow of the entrance of the infection. In some the mucous membrane undoubtedly offers an excellent medium for the growth of the virus, and as it sinks deep into the interstices of this surface, it produces local irritation and reaction which open the way for its deeper penetration. Immediate irrigation of the part will frequently prevent these local lesions and therefore presumably the surface tissues have not been penetrated at the time of contact, or if so, very superficially, and the virus may be killed or removed before it has a chance to become entrenched in the deeper tissues. There is another group in which the infectious agents are carried to and deposited on the surface of the skin by lice, ticks and fleas. Either through the bites of these insects or through scratching caused by the local irritation, the virus gains entrance through these superficial abrasions. In still another group the infection is directly inoculated into the blood stream by blood sucking insects such as mosquitoes and sand flies. Finally there is a small group of cases in which the portal of entry cannot be explained by any of these means. All of these diseases may be grouped as shown in Table XVIII.

TABLE XVIII

<i>Skin Abrasions or via a Mucous Membrane</i>	<i>Blood Sucking Insects</i>
Staphylococcal septicemia	Malaria fever
Streptococcal septicemia	Yellow fever (see page 130)
Erysipelas	Filariasis
Syphilis	Dengue
Yaws	Pappataci
Lymphogranuloma inguinale	Leishmaniasis
Gonorrhea	Kala azar
Tularemia	Oriental sore
Anthrax	Leishmaniasis
Glanders	Chagrin disease
Tetanus	Trypanosomiasis
Foot and mouth disease	African sleeping sickness
	Chagrin disease
<i>Animal Bites</i>	<i>Unclassified</i>
Rabies	Smallpox
Rat bite fever	Varicella
	Herpes zoster
<i>Lice Ticks and Fleas</i>	Lymphocytic choriomeningitis
Typhus fever	Leptospirosis
Tsutsugamushi disease	Infectious mononucleosis
Trench fever	Epidemic pleurodynia
Rocky Mountain fever	Toxoplasmosis
Relapsing fever	Erythematosis
Plague	Lupus erythematosus
Swineherd's disease	
Q fever	
Bull's fever	
Colorado tick fever	
Rickettsialpox	

## SEPTICEMIA

**Definition**—An exact definition of septicemia is difficult as it is a clinical symptom complex or syndrome which may be due to many different bacteria. There are certain closely related terms applied to different phases or states resulting from bacterial causes of disease that it might be well first to be clear about.



*Toxemia* should be reserved for those conditions where an endotoxin or an exotoxin produces symptoms but the bacteria do not invade the blood stream or specific tissues, but the toxins do, as diphtheria toxemia and tetanus toxemia.

*Pyemia* should be applied where abscesses or purulent collections occur in the fixed tissues. If these are scattered and cannot be accounted for by lymphatic spread the organisms must have been carried by the blood stream but this may not be capable of bacteriological proof nor may there be any evidence to indicate that the bacteria grow in the blood or within the blood vessels.

*Septicemia* is a state in which organisms are in the blood on occasion but even if not demonstrable by bacteriological methods they are suspected of being disseminated. The principal feature however is a severe general toxic reaction often characterized by chills and even rigors. This category does not necessarily include the group of specific infections mentioned elsewhere although severe toxic symptoms may also be present. The most outstanding examples are found in instances where the blood vessels (veins) are the source of a blood stream infection.

*Bacteremia* should be strictly applied to those states where bacteria are recovered from the blood stream. There may be either a pyemia or a septicemia present. On the other hand there may be comparatively little or no evidence of either.

There are a number of specific diseases in which the organisms can be grown from (or seen in) the blood either during the early stages of the infection, or periodically during its course, such as typhoid fever, pneumonia, meningococcal meningitis, anthrax, glanders, undulant fever, relapsing fever, subacute bacterial endocarditis (lenta), etc. These can all be classed as septicemias and some as pyemias as well, but on the other hand they are also clinically specific infectious diseases. If the organisms were found in the blood stream and there were not the specific clinical manifestations of the disease, then they would properly be called bacteremias.

**Etiology—General**—Man is being constantly exposed to invasion by bacteria and there is little doubt that fleeting bacteremias occur without causing any clinically recognizable symptoms. On the other hand for no accountable reason they may be assailed by organisms which they have been harboring on their skin and mucous membranes as harmless parasites. There are however certain contributing factors which may play a role in this warfare. These infections are more common in the old and the young, in cold weather rather than in the summer, in the late winter rather than in the autumn, in chronic alcoholics in such diseases as diabetes mellitus, cardiorenal disease, arterio-sclerosis, cirrhosis of the liver, cancer where there has been undernutrition, exhausting labor or great mental anxiety or worry. They are more common in women on account of puerperal sepsis. The blood and associated protective cells undoubtedly can usually cope with a mild bacterial invasion but why they cannot do so always is not wholly known as our knowledge of acquired and natural immunity against infection is still incomplete. It is known that the blood possesses certain bactericidal powers and also affords some important aid to the leucocytes and to the fixed cells in the reticulo-endothelial system of the spleen.

liver, bone marrow and lymph glands to carry on their work of phagocytosis and destruction of bacteria. Apparently at these periods of susceptibility there is not only a reduction in the protective properties of the blood, but also through some unknown effect the cells cannot properly fulfill their duty. It may be due to their debility, intoxication, fatigue, lack of response to stimulation or something else—we do not know, and leaves room for much speculation. It is known, however, that in many of these cases the humoral protective bodies in the leucocytes are in abnormally small amounts or totally absent.

**Specific**—The bacteria which produce a septicæmia are numerous, and it is not our purpose to discuss them all in detail. The more important are the following: hemolytic streptococci, nonhemolytic streptococci, pneumococci, staphylococci, meningococci, gonococci, *B. coli*, *B. pyocyaneus*, *B. mucosus capulatus*, *H. influenzae*, *B. proteus*, *B. faecalis alcaligenes* etc. Of these the first seven are the most important. Some of them have been considered under acute and subacute endocarditis where the principal lesion may be situated or where it is but an incidental finding.

**Symptoms and Signs**—It is not the present purpose to deal with all forms of septicæmia. There are two, however, of great importance which require special mention, namely the streptococcus and staphylococcus. The general clinical characters of the other nonspecific organisms are similar to these. The incubation period varies considerably but as a rule does not exceed a few days except when the septicæmia follows upon a chronic infection when it is totally unknown. The portals of entry are similar for both with occasional emphasis on a certain route for one or other of them.

- 1 Skin wounds—varying from a scratch to large denuded areas (staphylococcus)
- 2 Puerperal uterine infections (streptococcus)
- 3 Paronychia, boils, carbuncles, bed sores and burns (staphylococcus)
- 4 Otitis media, mastoiditis, lateral sinus thrombosis (streptococcus)
- 5 Ethmoiditis and sphenoiditis (streptococcus)
- 6 Tonsillar infections, particularly scarlet fever and septic sore throat (streptococcus)
- 7 Alveolar abscesses (streptococcus)

When a septicæmia occurs in the course of empyema, osteomyelitis, pyelitis, etc., these might be designated as portals of entry, but they are not strictly so, as the septicæmia is but a feature of the infection. However this might also be held with equal reason for most of those mentioned above if we are to be strictly logical. It may now be asked why a septicæmia should arise from such slight causes as some of those mentioned. The answer is quite obvious in some. In puerperal sepsis there are infected thromboses in the uterine veins; also there is an intravascular infection in lateral sinus thrombosis. If this is not present or there is no infected thrombus in some of the veins draining the infected mastoid or ear, the septicæmia will cease as soon as these latter are cleared out, and similarly in ethmoiditis and sphenoiditis. In fact in most cases of septicæmia a local infected thrombosis will be found at the portal of entry. It may be extremely small and the wound may be healed without its presence.

being suspected. It is doubtful whether a septicemia will continue if this is not the case. In other words bacteria seldom persist in the blood stream unless renewed from some such source or from a focus on the endocardium as in bacterial endocarditis. This is particularly the case in small skin wounds.

The most important clinical feature of these infections is pyrexia. This is usually of the septic type that is intermittent. However this is not at all constant and there may be periods of apyrexia. Chills and rigors are common and may occur with such regularity as to suggest malaria. There are frequent sweats and great thirst. The heart rate is rapid and the respirations may be slightly accelerated in proportion to the pyrexia but this is not conspicuous unless pneumonia develops when typical tachypnea appears. There is a leucocytosis due to increase of polymorphonuclear cells and the spleen is enlarged and usually palpable. There are the other usual signs of infection headache malaise, general pains, and exhaustion. A rapid anemia is common. Erythemas are frequent in septicemia as is also purpura. These have already been described in both infections under bacterial endocarditis (see Chapter VII). Metastatic abscesses are not common with the streptococcus but are with the staphylococcus. These may occur in any tissues but especially in the lungs, spleen and kidneys. In both a metastatic pneumonitis is common. Jaundice is frequent as is hematuria. A true nephritis is more common with the streptococcus and pyelonephritis with the staphylococcus.

**Course**—The course varies greatly. In staphylococcus septicemia in children death may occur within forty eight hours. Such cases are classed as fulminating and occur in other infections before specific signs appear as in epidemics of influenza meningitis scarlet fever septic sore throat etc. The majority of cases last longer and may be classed as the acute type while a small number may continue for weeks and even months and are called chronic. The duration is determined by the virulence of the organism and the resistance of the host. The disease usually terminates by exhaustion with coma and the other signs of intense intoxication. Local abscesses in the brain lungs liver or kidneys may modify the course.

**Diagnosis**—The presence of a general infection is usually readily recognized and the majority soon exhibit the special features which lead to their identification as a specific disease. In others this may be delayed for some time as in typhoid and undulant fever. Although a septicemia may be suspected and even a shrewd guess made as to the particular organism causing it the correct diagnosis can only be proved by the bacteriological examination of the blood. This should not rest on one examination only but if negative the first time it should be repeated. In such cases cooperation and consultation between the clinician and bacteriologist are imperative if satisfactory results are to be obtained. All the facts should be given to the latter who should see the case frequently with the clinician. All bacteria do not grow equally well on the same media and some require quite a specific environment. This is within the knowledge of the bacteriologist who must be governed by the probabilities indicated. Urine cultures may also be helpful.

**Prognosis**—This has been to some extent indicated under the course of the disease. All cases are by no means fatal especially streptococcal septic

**emia** Although it is the more common and more deaths occur from it, there are also many more recoveries, in fact it is likely that many recover without being recognized. True staphylococcal septicemia is relatively uncommon but up to the last few years the mortality was almost 100 per cent. There is no doubt again that some of these are not recognized and may recover, especially the more chronic cases in whom multiple abscesses form. These may continue to appear with intermittently positive blood cultures. In such it is certain that all foci have not been detected. These are usually metastatic. The outcome is also governed by prompt, energetic and rational treatment which primarily depends upon early bacteriological diagnosis.

**Treatment**—To recount all of the measures which have been advocated for the treatment of septicemia would not only be impossible but worse than useless. It is obvious that the usual general measures used in the treatment of any general infection should be employed, particularly rest, a diet of sufficient calories, and abundant fluids by mouth, and intravenously or per rectum if necessary. Pyrexia and nervous symptoms should be controlled by hydrotherapy. *Surgical measures* are indicated to effect free drainage of all approachable purulent collections as in mastoiditis, otitis media, sphenoiditis, ethmoiditis, empyema, osteomyelitis, suppurating wounds, cellulitis, carbuncles, etc. If the portal of entry is in the skin and is of small area as in some cases of staphylococcal septicemia in children, it should be excised rather than incised, so removing the whole of the infected area including the small veins immediately draining it. A small thrombophlebitis one cm long may be the cause of a fatal infection. Healthy tissue should not otherwise be invaded by surgical methods. Trauma to the surrounding tissues should be avoided at all costs. The local reaction about the suppurating area should be left intact as it is an attempt to localize the infection but the necrotic and suppurating contents should be removed by all means at our command and localized pockets opened for free drainage. Heat should be applied in the form of hot saline or hypertonic packs and frequently renewed so as to promote a free serous discharge. All sinuses should be kept open and draining freely. The chemotherapeutic and antibiotic treatment of septicemias depend upon the specific organism causing the disease. As stated in preceding pages these methods of therapy will be dealt with in a separate chapter (see Chapter XX).

## ERYSIPELAS

**Synonym**—St. Anthony's fire

**Definition**—Erysipelas is a specific disease of the skin caused by the hemolytic streptococcus and is characterized by a spreading erythematous edema with a clear cut margin.

**Etiology**—Erysipelas is not as common today as in years gone by when it was much dreaded particularly in surgical practice when epidemics especially in hospitals were frequent. It is not caused as was one time thought by a specific strain of streptococcus but may be due to any one of several types of Group A streptococcus. It was at one time thought that strains of the organism which caused erysipelas produced a specific toxin for this dis-

ease. This concept has now been discarded. It is more common in women than in men, and during the middle decades. Acute illnesses, operation, chronic diseases and alcoholism predispose to its occurrence. In fact those conditions which seem to render septicemia more liable are also influential in the present instance.

**Symptoms and Signs**—The incubation period as in all streptococcal infections is about three days. The portal of entry is through a skin wound although this may be such a small break in its continuity as to be invisible. On the other hand it commonly developed about a surgical wound. This is rare today. The onset is sudden but not usually explosive with a chill and rigors. There is malaise, headache, anorexia and pyrexia. This last may be high without definite character, as it is either continuous or remittent, but never intermittent.



Fig. 464—Erysipelas of the face showing characteristic edema. (From Sutton and Sutton, Diseases of the Skin.)

The most frequent site is the face particularly on the nose from which it spreads over the cheeks in a butterfly like distribution. It may, however, occur on any part of the skin as about the umbilicus in the newborn, the vulva in the puerperium, around chronic ulcers, operation wounds or in the nasal and nasopharyngeal mucous membrane in association with sinus and tonsillar infections.

The appearance of the lesion is quite characteristic wherever it occurs. The skin is bright red and there is a swollen or edematous clear cut slightly elevated margin which slowly creeps into the surrounding tissues while the older areas show definite improvement. The periphery may be indented from fingerlike protrusions which represent the irregular progress of the infection along the skin lymphatics. There may be multiple sites of infection either proximal when they may unite to form a more irregular lesion or on distant areas such as the face and the leg or the vulva and other areas which have no relation to each other except as being simultaneous portals of

**cemia** Although it is the more common and more deaths occur from it, there are also many more recoveries, in fact it is likely that many recover without being recognized. True staphylococcal septicemia is relatively uncommon but up to the last few years the mortality was almost 100 per cent. There is no doubt again that some of these are not recognized and may recover, especially the more chronic cases in whom multiple abscesses form. These may continue to appear with intermittently positive blood cultures. In such it is certain that all foci have not been detected. These are usually metastatic. The outcome is also governed by prompt energetic and rational treatment which primarily depends upon early bacteriological diagnosis.

**Treatment**—To recount all of the measures which have been advocated for the treatment of septicemia would not only be impossible but worse than useless. It is obvious that the usual general measures used in the treatment of any general infection should be employed, particularly rest, a diet of sufficient calories, and abundant fluids by mouth, and intravenously or per rectum if necessary. Pyrexia and nervous symptoms should be controlled by hydrotherapy. *Surgical measures* are indicated to effect free drainage of all approachable purulent collections as in mastoiditis, otitis media sphenoiditis, ethmoiditis, empyema, osteomyelitis, suppurating wounds, cellulitis, carbuncles, etc. If the portal of entry is in the skin and is of small area as in some cases of staphylococcal septicemia in children it should be excised rather than incised so removing the whole of the infected area including the small veins immediately draining it. A small thrombophlebitis one cm long may be the cause of a fatal infection. Healthy tissue should not otherwise be invaded by surgical methods. Trauma to the surrounding tissues should be avoided at all costs. The local reaction about the suppurating area should be left intact as it is an attempt to localize the infection but the necrotic and suppurating contents should be removed by all means at our command, and localized pockets opened for free drainage. Heat should be applied in the form of hot saline or hypertonic packs and frequently renewed so as to promote a free serous discharge. All sinuses should be kept open and draining freely. The chemotherapeutic and antibiotic treatment of septicemias depend upon the specific organism causing the disease. As stated in preceding pages these methods of therapy will be dealt with in a separate chapter (see Chapter XX).

## ERYSIPELAS

**Synonym**—St Anthony's fire

**Definition**—Erysipelas is a specific disease of the skin caused by the hemolytic streptococcus and is characterized by a spreading erythematous edema with a clear cut margin.

**Etiology**—Erysipelas is not as common today as in years gone by when it was much dreaded particularly in surgical practice when epidemics especially in hospitals were frequent. It is not caused as was one time thought by a specific strain of streptococcus but may be due to any one of several types of Group A streptococcus. It was at one time thought that strains of the organism which caused erysipelas produced a specific toxin for this dis-

All attempts at specific therapy with *sera* have now been superseded by sulfonimides and penicillin particularly sulfadiazine which usually controls the infections in 36 to 48 hours (see Chapter XX)

## SYPHILIS

**Synonym**—*Lues venerea*

**Definition**—This is an acute and chronic disease due to a specific organism of the spirochete species called the *Treponema pallidum*. It is a disease which probably has been existent for many centuries, but it occurred in epidemic form in the sixteenth century, closely following the return of Columbus from his voyages to the West Indies.

**Etiology**—It is difficult to obtain accurate figures as to its incidence in the population of North America at the present time. It is noted that it is more common among the Negroes than among the whites. Such statistics as are available would indicate that the incidence varies from 5 to 25 per cent in an ordinary hospital population. Perhaps on the whole 10 per cent would be a fairly accurate estimate.

The *Treponema pallidum* is a delicate spiral with from six to ten turns, and its total length is about 10 microns. The spirals are regular and the movement of the organism is a rotating one around its long axis. It is extremely labile and is killed by simple soap and water drying, and exposure to even the weakest disinfectants. It has not as yet been grown on artificial medium but can be transmitted from animal to animal by direct inoculation. It is found in large numbers in the tissue juices of the local lesions. It is not stained readily but is best demonstrated by Giemsa's solution or the Fontana silver method. A simple manner of demonstrating them is by making a mixture of a little of the tissue juice with Gunther's India ink on a glass slide and allowing it to dry. Under the oil immersion the *Treponema* will be seen as fine white spirals on a black background. They are most readily detected in the tissue juice when examined with dark field illumination.

The spirochete is transmitted from man to man by direct contact although occasionally it has been reported as being conveyed by musical instruments drinking cups hypodermic needles, blood transfusions etc. The inoculation may occur on any cutaneous or exposed mucous surface. The most frequent manner of inoculation is during sexual intercourse and as will be seen later the portal of entry is more easily recognized in the male than in the female. Another important and common means of transmission is by kissing or through human bites. Doctors and nurses are sometimes inoculated on the hands through contamination with syphilitic exudate. This was more common before rubber gloves were so much in vogue. Suckling infants have been known to be infected through a syphilitic lesion upon the nipple of a wet nurse. Although the venereal contact is the most common method of inoculation there are areas in the world where this disease is supposed to be endemic and practically the whole of the population is infected in childhood. In these places it is not a venereal but an ordinary contagious disease. This is particularly true in certain parts of Arabia where 90 per cent of the population

infection. The mucous membranes are sometimes involved but much less frequently than the skin. Although it spreads from the mucous membranes to the skin, the reverse is exceedingly rare. The larynx is rarely involved, but if so, usually causes death from suffocation. When it spreads from the vulva to the vagina and endometrium a fatal septicemia is the rule. Bullae and vesicles often develop over the more acute portions of the skin lesion, and sometimes local suppuration due to secondary infections or extensions to the subcutaneous tissues occur while gangrene is rare. The neighboring lymph nodes are usually enlarged but rarely suppurate. Extension to adjacent tissues such as the orbit and from thence to the meninges and cavernous sinus, or into the paranasal sinuses occasionally happens.

The constitutional symptoms may be extreme with great prostration and delirium particularly at night. There is a leucocytosis and the spleen is enlarged but seldom palpable. The urine contains a trace of albumin and a few casts while nephritis occasionally occurs (one per cent).

A bacteremia is unusual but when it does occur, metastatic lesions such as endocarditis, arthritis, pericarditis, pneumonia, pleurisy and phlebitis may develop.

**Pathological Anatomy**—The streptococci are found in the lymphatics of the skin along the advancing margin, but are absent in the other parts of the lesion. Surrounding the lymph channels there is an intense infiltration with mononuclear cells. Visceral changes such as cloudy swelling common to all infections are found but when there is a bacteremia, local lesions also may develop.

**Diagnosis**—This is usually done by inspection, but it must be differentiated from a simple local erythema which, however, does not have a raised margin. Acute eczema or dermatitis may suggest erysipelas, but there is no pyrexia or systemic symptoms. Cutaneous phlegmon may be more difficult to exclude but there is usually a much deeper inflammation with brawny induration and not the clear cut edematous margin found in erysipelas.

**Course and Prognosis**—The duration of the disease is indefinite. It may creep over large areas and indeed may eventually cover the greater part of the body. As it spreads the older areas subside. Relapses and recurrences are common and it may recur year after year at the same time and the same place or may be associated with some periodic occurrence such as menstruation. When an area of skin is frequently involved there may develop permanent blockage of the lymphatics leading to a local elephantiac condition. Usually the disease lasts but a few weeks and complete recovery results. The mortality varies being reported by different authorities as from 5 to 10 per cent. The age and previous condition of the patient greatly modify this. In previously healthy adults it is less than 1 per cent, but when blood cultures are positive it is close to 100 per cent.

**Treatment**—The general treatment of this disease follows the same principles as for other infections, namely, bed rest, high caloric and protein diet, large amounts of fluids. The pyrexia and nervous symptoms should be controlled by hydrotherapy. The local lesion should be kept clean and the pain relieved by hot or cold applications.



**Primary Symptoms and Signs**—The incubation period is from ten to sixty days, usually about twenty one days. During this period there are few or no symptoms. The chancre may develop on many extragenital sites such as the finger, the tongue, the lip, the tonsil, the mons veneris, lower abdomen, eyelid, nipple, etc. It is usually single although occasionally two chancres may be found particularly on contiguous mucous membranes. It is painless and without irritation. It heals slowly when untreated, leaving a pigmented scar which may be visible for many months, but this in time completely disappears or may leave a smooth whitish surface. Recurrent chancre or *chancre redux* results from *Treponema* remaining viable in the scar. There are seldom any general symptoms during the early period of the chancre, but with the invasion of the blood and dissemination of the spirochete, symptoms of a generalized infection such as malaise, chilliness, pyrexia, may be more or less prominent incident with its massive destruction. In addition to the local lymphatic enlargement a general adenopathy occurs. There is also some anemia which



Fig. 46.—Chancre of the penis with widespread edema. (From Sutton and Sutton, *Diseases of the Skin*.)

may be extreme. Generalized pains in the bones and joints may be a prominent feature. In many cases these symptoms are entirely absent, while in others they may assume a virulent character giving all the evidences of a severe general infection. The spleen may be palpable with icterus and enlargement of the liver. The interval between the appearance of the chancre and the development of these general symptoms is called the secondary incubation period. It may vary considerably in duration.

**Secondary Symptoms and Signs**—With its termination and the appearance of the general toxic reaction acute lesions in many organs may develop such as iritis, meningitis, valvulitis, and diffuse and variegated skin eruptions. The latter at one time attracted considerable attention and made syphilis practically a dermatological disease. At that time the general nature of the infection was not appreciated as it has been since the demonstration of its definitely infectious and systemic character. There is hardly a dermatological manifestation which cannot be simulated by syphilis. There are a few important points which should suggest the syphilitic nature of skin eruptions. They are usually painless and not itchy. They are apt to infiltrate centrifu-

are syphilitic. It is acquired in childhood, is nonvenereal and is called "bejel," and is distinguished by these people from *franghi* or the "foreign disease."

It may be transmitted from a syphilitic mother to the fetus. This is known as congenital syphilis. *Treponema* have been proved to be present in the semen of latent syphilitics, but whether such can infect the ovum without its also infecting the mother first is open to considerable question.

At the point of inoculation there is probably a slight abrasion of the epithelium through which the *Treponema* penetrate. They may pass from here to the general circulation without producing a local reaction recognizable by the patient, or it may be so insignificant as to be considered of no importance, and a patient may quite conscientiously state that he has never to his knowledge been so infected. In women this must be particularly common as the primary lesion within the vagina or on the cervix uteri may pass unnoticed, and similarly extremely mild reactions occurring on the labia minora, and less frequently on the labia majora attract but little attention. The characteristic primary lesion is a hard, sclerosing nodule which on account of its cartilaginous firmness is called a chancre, or hard sore, as distinguished from the chancroid or soft sore which although venereal, is not syphilitic. It may remain as a small hard papule but usually the surface ulcerates, leaving a clear cut, crater like depression. This ulceration may be serpiginous or even gangrenous (see Fig. 465). They are indolent in healing unless treated.

**Pathological Anatomy**—The primary lesion is quite characteristic. There is infiltration with leucocytes, lymphocytes and plasma cells in the perivascular tissues of the smallest blood and lymph vessels followed by an endovasculitis eventually affecting the intima and leading to obliteration of their lumen. There is an overgrowth of connective tissue with spindle cells, epithelial cells and a few giant cells. The lesion will be found to contain large numbers of *Treponema* which may invade the blood stream and be carried throughout the circulation. Others enter the lymphatics and travel to the regional lymph glands most commonly to those in the inguinal area. These may become enlarged and hard but eventually return to about their normal size without further local lesion. In rare cases necrosis and suppuration occur, the gland softens and eventually discharges through the skin but gonorrhea and lymphopathia venereum must be excluded. These are called buboes. Probably before the chancre has fully developed the *Treponema* have passed beyond it and have either invaded the blood stream or the lymphatics. This widespread distribution of the spirochete may lead to the so called "secondary" or disseminated lesions which usually regress and in some the "tertiary" or granulomatous lesions develop. The anatomical changes of these will be discussed later. In many individuals infected with syphilis neither primary, secondary or tertiary lesions can be found at autopsy indicating, as in tuberculosis, that a local lesion need not necessarily be a general one or at least that a general dissemination of the spirochete need not produce generalized lesions. This would suggest that the *Treponema* may be destroyed in the tissues without causing any anatomical change.

due to the dilatation of the capillaries which contain large numbers of *Treponema* and the tissue juice from such is highly contagious. There is another macular eruption which may occur at the same time or somewhat later, which is more elevated and instead of being rose colored is a coppery brown. These lesions result from more pronounced pericapillary and capillary infiltration, and persist longer and often leave a definitely pigmented area, or in the darker races areas lighter than the surrounding skin.



Fig. 458.—Grouped, or coriaceous papulo-queous syphilitic eruption of six weeks duration. (Courtesy of Dr. J. B. Shelmire. From Sutton and Sutton, Diseases of the Skin.)

The next eruptions are papular. These vary in size from a pinhead to the size of a nickel. They are definitely elevated and are due to a still more extensive productive lesion with considerable vascular and perivascular infiltration. They appear not only on the torso but on the scalp where they lead to a moth-eaten alopecia on the palms of the hands and the soles of the feet where there is a tendency for them to become dry and cracked which may lead to ulceration. They may also occur in the nails producing syphilitic onychia and perionychia. All these lesions contain large numbers of *Treponema* but if they do not ulcerate or macerate are not as infectious as are the macular and roseolar lesions. They occur however in considerable num-

gally and disappear centrally, thus giving a roughly ringlike appearance to some and an umbilicated appearance to others. The first eruption is usually of a macular or roseolar character which is highly infectious in moist areas (mucous patches). It is distributed mostly over the chest and abdomen. It may vary in intensity from a diffuse blush to definite rosy macules. It is



Fig. 466.—Maculopapular syphiloderm of trunk. (From Sutton and Sutton. Diseases of the Skin.)



Fig. 467.—Papulopustular syphilodermata in a neglected case of lu. (Courtesy of Dr. C. H. Leslie Castle. From Sutton and Sutton. Diseases of the Skin.)

due to the dilatation of the capillaries which contain large numbers of *Treponema* and the tissue juice from such is highly contagious. There is another macular eruption which may occur at the same time or somewhat later which is more elevated and instead of being rose colored is a coppery brown. These lesions result from more pronounced pericapillary and capillary infiltration, and persist longer and often leave a definitely pigmented area, or in the darker races areas lighter than the surrounding skin.



Fig. 488.—Grouped or erythematous papulo-quantous syphilitic of six weeks duration. (Courtesy of Dr. J. B. Sheline. From Sutton and Sutton, Diseases of the Skin.)

The next eruptions are papular. These vary in size from a pinhead to the size of a nickel. They are definitely elevated and are due to a still more extensive productive lesion with considerable vascular and perivascular infiltration. They appear not only on the torso but on the scalp where they lead to a moth-eaten alopecia on the palms of the hands and the soles of the feet where there is a tendency for them to become dry and cracked which may lead to ulceration. They may also occur in the nails producing syphilitic onychia and perionychia. All these lesions contain large numbers of *Treponema* but if they do not ulcerate or macerate are not as infectious as are the macular and roseolar lesions. They occur however in considerable num-

bers around the genitals and anus where on account of the local moisture maceration occurs. These are called condylomata and are extremely infectious, as are similar lesions upon the mucous membranes of the lip, buccal cavity, and tongue. These are called mucous patches. The presence of these lesions and of a primary chancre about the mouth account for the frequent inoculation of noninfected individuals by kissing. This papular eruption may become infected and form pustules, and is then called a "pustular syphilide." They may resemble acne, impetigo, variola, or may involve the skin in extensive suppuration. An eruption of still later development is nodular or

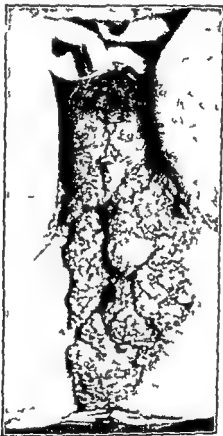


Fig. 469.—Condylomata of vulva and perineum. (Courtesy of Drs. Fordyce and Mackee. From Sutton and Sutton. *Diseases of the Skin*.)

tubercular syphilide. It is an elevated nodule with a cyanotic reddish color, and has the common attribute of the majority of syphilides in appearing in circles with a serpiginous progression. When they heal they leave a distinct depression due to destruction of tissue with a brownish appearance. The tubercles may be so numerous as to coalesce, involving large areas and they may ulcerate. They are usually very persistent. This tubercular eruption seems to occupy a position midway between the true secondary lesions in which there is not a pronounced cellular reaction and destruction, and the last or tertiary syphilitic lesion called the "gumma." These are more deep seated lesions appearing in the skin, mucous membrane and viscera which ulcerate and lead to large areas of central necrosis. They are extremely indolent and destructive when untreated.

**Tertiary Symptoms and Signs** —So far the superficial lesions of syphilis only have been described. It will be noted that there is a gradation between the early macular or roseolar lesions and the more deep seated and destructive gummata. These however are but a few of the descriptive terms that may be applied to syphilitic dermatological lesions. The other terms give a faint idea of the varieties of eruption that may be encountered, such as papulosquamosa of the palm of the hand, papulopustulosa, papuloorbicularis, circinata, miliopapulosa or lichenoids, the leucodermata which appear so characteristically on the back and sides of the neck and may lead to a correct diagnosis on sight, the maligna or rupia frambesiformis, corymbiformis, tuberoserpiginosa, ulceroserpiginosa, diffuse lingual gumma. In addition to the skin the mucous membrane of the mouth, pharynx, nose, tonsils, and larynx may be involved in similar lesions.



Fig 46—Squamous syphilite of palm. (From Sutton and Sutton Diseases of the Skin)

As the *Treponema pallidum* is distributed to all tissues where there are capillaries syphilitic lesions may there develop. Therefore it is an exhaustive procedure to describe them all in detail. They have already been dealt with under lesions of the heart and blood vessels, the esophagus, stomach, intestines, liver and organs of the genitourinary tract, the nervous system, etc. It would serve no useful purpose to recapitulate these here. It may be stated as an axiom that syphilis should be considered the possible cause of every chronic lesion or group of symptoms until proved to the contrary. There are a few however which should be emphasized.

Headache and pains in the bones which are particularly severe at night should be suspected as being syphilitic. The lesion may be in the form of

bers around the genitals and anus where on account of the local moisture maceration occurs. These are called condylomata and are extremely infectious as are similar lesions upon the mucous membranes of the lip, buccal cavity, and tongue. These are called mucous patches. The presence of these lesions and of a primary chancre about the mouth account for the frequent inoculation of noninfected individuals by kissing. This papular eruption may become infected and form pustules, and is then called a "pustular syphilide." They may resemble acne, impetigo, variola, or may involve the skin in extensive suppuration. An eruption of still later development is a nodular or



Fig. 469—Condylomata of vulva and perineum. (Courtesy of Dr. Forlyce and Mackee. From Sutton and Sutton, Diseases of the Skin.)

tubercular syphilide. It is an elevated nodule with a cyanotic reddish color and has the common attribute of the majority of syphilides in appearing in circles with a serpiginous progression. When they heal they leave a distinct depression due to destruction of tissue with a brownish appearance. The tubercles may be so numerous as to coalesce involving large areas and they may ulcerate. They are usually very persistent. This tubercular eruption seems to occupy a position midway between the true secondary lesions in which there is not a pronounced cellular reaction and destruction, and the last or tertiary syphilitic lesion called the "gumma." These are more deep seated lesions appearing in the skin, mucous membrane and viscera which ulcerate and lead to large areas of central necrosis. They are extremely indolent and destructive when untreated.



communicate between the tables of the cranium. Syphilitic arthritis closely resembles tuberculosis and may be a true syphilitic lesion of the joints differing from the trophic destruction commonly known as Charcot's joint which occurs in locomotor ataxia and syringomyelia.

All of these syphilitic lesions no matter where they may appear, are due to the localized syphilitic reaction about the small blood vessels. It is true that some tissues are more often involved than others particularly the

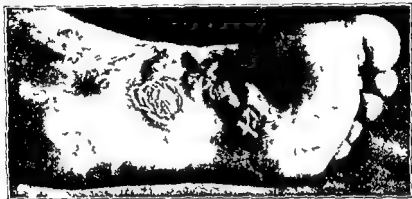


Fig 4 —Syphilitic bullous eruption of the skin. (From Sutton and Sutton Diseases of the Skin)

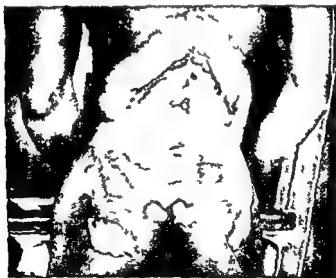


Fig 4 3—Deep, following syphilitic ulceration of the skin in a Negro. (From Sutton and Sutton Diseases of the Skin)

skin the aortic valves the aorta, the liver, the bones and the eye while in other tissues syphilitic lesions are comparatively rare. There is however one system in which prominent and progressive lesions are common namely the nervous system. In conformity with syphilis elsewhere the blood vessels of the meninges and parenchyma of the central nervous system may be involved and produce one or more of several clinical patterns. These are not always

vascular obliteration, necrosis leading to osteitis, and osteomyelitis with discharging sinuses. Periosteitis of the long bones, particularly of the tibia usually produces an extensive productive lesion causing the so called "sabre shin." It is at first an acute lesion with pain, swelling, tenderness, and redness. These syphilitic bone lesions are among the few that produce pain. Local exostoses may also occur. Gummata sometimes produce extensive destruction of the bone and a spontaneous fracture may occur. Small gummata

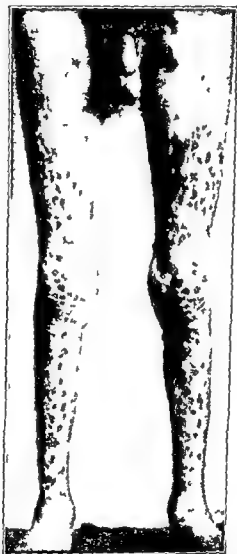


Fig. 471.—Rupia syphilitica

(Courtesy of Dr. Otto Leslie Castle. From Sutton and Sutton, Diseases of the Skin.)

usually pass unnoticed although they may leave an area of absorption recognizable by x ray. A syphilitic spondylitis may produce stiffness of the spine and deformity. Destructive lesions of the bones of the face and nose are also due to gummata and there may be a complete collapse of the nasal structure giving rise to a characteristic deformity (see Fig. 1). There may also be perforation of the hard and soft palate. Punched out syphilitic ulcers of the scalp or cranium are quite characteristic. They are usually multiple and may

2021年11月1日 星期一  
 2021年11月2日 星期二  
 2021年11月3日 星期三  
 2021年11月4日 星期四  
 2021年11月5日 星期五  
 2021年11月6日 星期六  
 2021年11月7日 星期日  
 2021年11月8日 星期一  
 2021年11月9日 星期二  
 2021年11月10日 星期三  
 2021年11月11日 星期四  
 2021年11月12日 星期五  
 2021年11月13日 星期六  
 2021年11月14日 星期日  
 2021年11月15日 星期一  
 2021年11月16日 星期二  
 2021年11月17日 星期三  
 2021年11月18日 星期四  
 2021年11月19日 星期五  
 2021年11月20日 星期六  
 2021年11月21日 星期日  
 2021年11月22日 星期一  
 2021年11月23日 星期二  
 2021年11月24日 星期三  
 2021年11月25日 星期四  
 2021年11月26日 星期五  
 2021年11月27日 星期六  
 2021年11月28日 星期日  
 2021年11月29日 星期一  
 2021年11月30日 星期二

1. *Phragmites australis* (Cav.) Trin. ex Steud.  
 2. *Scirpus americanus* (L.) Pers.  
 3. *Eleocharis acicularis* (L.) Rostk Schmidt  
 4. *Sagittaria arifolia* (L.) Link.  
 5. *Alisma plantago-aquatica* (L.) Rostk Schmidt  
 6. *Sparganium angustifolium* Michx.  
 7. *Najas* sp.  
 8. *Chara* sp.  
 9. *Utricularia* sp.  
 10. *Hydrocotyle* sp.  
 11. *Salvinia* sp.  
 12. *Wolffia* sp.  
 13. *Elodea canadensis* (Mill.) B. S. P.  
 14. *Hydrilla verticillata* (L.) Rostk Schmidt  
 15. *Valoniopsis spiralis* (L.) Rostk Schmidt  
 16. *Callitriche* sp.  
 17. *Utricularia* sp.  
 18. *Hydrocotyle* sp.  
 19. *Salvinia* sp.  
 20. *Wolffia* sp.  
 21. *Elodea canadensis* (Mill.) B. S. P.  
 22. *Hydrilla verticillata* (L.) Rostk Schmidt  
 23. *Valoniopsis spiralis* (L.) Rostk Schmidt  
 24. *Callitriche* sp.  
 25. *Utricularia* sp.  
 26. *Hydrocotyle* sp.  
 27. *Salvinia* sp.  
 28. *Wolffia* sp.  
 29. *Elodea canadensis* (Mill.) B. S. P.  
 30. *Hydrilla verticillata* (L.) Rostk Schmidt  
 31. *Valoniopsis spiralis* (L.) Rostk Schmidt  
 32. *Callitriche* sp.  
 33. *Utricularia* sp.  
 34. *Hydrocotyle* sp.  
 35. *Salvinia* sp.  
 36. *Wolffia* sp.  
 37. *Elodea canadensis* (Mill.) B. S. P.  
 38. *Hydrilla verticillata* (L.) Rostk Schmidt  
 39. *Valoniopsis spiralis* (L.) Rostk Schmidt  
 40. *Callitriche* sp.  
 41. *Utricularia* sp.  
 42. *Hydrocotyle* sp.  
 43. *Salvinia* sp.  
 44. *Wolffia* sp.  
 45. *Elodea canadensis* (Mill.) B. S. P.  
 46. *Hydrilla verticillata* (L.) Rostk Schmidt  
 47. *Valoniopsis spiralis* (L.) Rostk Schmidt  
 48. *Callitriche* sp.  
 49. *Utricularia* sp.  
 50. *Hydrocotyle* sp.  
 51. *Salvinia* sp.  
 52. *Wolffia* sp.  
 53. *Elodea canadensis* (Mill.) B. S. P.  
 54. *Hydrilla verticillata* (L.) Rostk Schmidt  
 55. *Valoniopsis spiralis* (L.) Rostk Schmidt  
 56. *Callitriche* sp.  
 57. *Utricularia* sp.  
 58. *Hydrocotyle* sp.  
 59. *Salvinia* sp.  
 60. *Wolffia* sp.  
 61. *Elodea canadensis* (Mill.) B. S. P.  
 62. *Hydrilla verticillata* (L.) Rostk Schmidt  
 63. *Valoniopsis spiralis* (L.) Rostk Schmidt  
 64. *Callitriche* sp.  
 65. *Utricularia* sp.  
 66. *Hydrocotyle* sp.  
 67. *Salvinia* sp.  
 68. *Wolffia* sp.  
 69. *Elodea canadensis* (Mill.) B. S. P.  
 70. *Hydrilla verticillata* (L.) Rostk Schmidt  
 71. *Valoniopsis spiralis* (L.) Rostk Schmidt  
 72. *Callitriche* sp.  
 73. *Utricularia* sp.  
 74. *Hydrocotyle* sp.  
 75. *Salvinia* sp.  
 76. *Wolffia* sp.  
 77. *Elodea canadensis* (Mill.) B. S. P.  
 78. *Hydrilla verticillata* (L.) Rostk Schmidt  
 79. *Valoniopsis spiralis* (L.) Rostk Schmidt  
 80. *Callitriche* sp.  
 81. *Utricularia* sp.  
 82. *Hydrocotyle* sp.  
 83. *Salvinia* sp.  
 84. *Wolffia* sp.  
 85. *Elodea canadensis* (Mill.) B. S. P.  
 86. *Hydrilla verticillata* (L.) Rostk Schmidt  
 87. *Valoniopsis spiralis* (L.) Rostk Schmidt  
 88. *Callitriche* sp.  
 89. *Utricularia* sp.  
 90. *Hydrocotyle* sp.  
 91. *Salvinia* sp.  
 92. *Wolffia* sp.  
 93. *Elodea canadensis* (Mill.) B. S. P.  
 94. *Hydrilla verticillata* (L.) Rostk Schmidt  
 95. *Valoniopsis spiralis* (L.) Rostk Schmidt  
 96. *Callitriche* sp.  
 97. *Utricularia* sp.  
 98. *Hydrocotyle* sp.  
 99. *Salvinia* sp.  
 100. *Wolffia* sp.  
 101. *Elodea canadensis* (Mill.) B. S. P.  
 102. *Hydrilla verticillata* (L.) Rostk Schmidt  
 103. *Valoniopsis spiralis* (L.) Rostk Schmidt  
 104. *Callitriche* sp.  
 105. *Utricularia* sp.  
 106. *Hydrocotyle* sp.  
 107. *Salvinia* sp.  
 108. *Wolffia* sp.  
 109. *Elodea canadensis* (Mill.) B. S. P.  
 110. *Hydrilla verticillata* (L.) Rostk Schmidt  
 111. *Valoniopsis spiralis* (L.) Rostk Schmidt  
 112. *Callitriche* sp.  
 113. *Utricularia* sp.  
 114. *Hydrocotyle* sp.  
 115. *Salvinia* sp.  
 116. *Wolffia* sp.  
 117. *Elodea canadensis* (Mill.) B. S. P.  
 118. *Hydrilla verticillata* (L.) Rostk Schmidt  
 119. *Valoniopsis spiralis* (L.) Rostk Schmidt  
 120. *Callitriche* sp.  
 121. *Utricularia* sp.  
 122. *Hydrocotyle* sp.  
 123. *Salvinia* sp.  
 124. *Wolffia* sp.  
 125. *Elodea canadensis* (Mill.) B. S. P.  
 126. *Hydrilla verticillata* (L.) Rostk Schmidt  
 127. *Valoniopsis spiralis* (L.) Rostk Schmidt  
 128. *Callitriche* sp.  
 129. *Utricularia* sp.  
 130. *Hydrocotyle* sp.  
 131. *Salvinia* sp.  
 132. *Wolffia* sp.  
 133. *Elodea canadensis* (Mill.) B. S. P.  
 134. *Hydrilla verticillata* (L.) Rostk Schmidt  
 135. *Valoniopsis spiralis* (L.) Rostk Schmidt  
 136. *Callitriche* sp.  
 137. *Utricularia* sp.  
 138. *Hydrocotyle* sp.  
 139. *Salvinia* sp.  
 140. *Wolffia* sp.  
 141. *Elodea canadensis* (Mill.) B. S. P.  
 142. *Hydrilla verticillata* (L.) Rostk Schmidt  
 143. *Valoniopsis spiralis* (L.) Rostk Schmidt  
 144. *Callitriche* sp.  
 145. *Utricularia* sp.  
 146. *Hydrocotyle* sp.  
 147. *Salvinia* sp.  
 148. *Wolffia* sp.  
 149. *Elodea canadensis* (Mill.) B. S. P.  
 150. *Hydrilla verticillata* (L.) Rostk Schmidt  
 151. *Valoniopsis spiralis* (L.) Rostk Schmidt  
 152. *Callitriche* sp.  
 153. *Utricularia* sp.  
 154. *Hydrocotyle* sp.  
 155. *Salvinia* sp.  
 156. *Wolffia* sp.  
 157. *Elodea canadensis* (Mill.) B. S. P.  
 158. *Hydrilla verticillata* (L.) Rostk Schmidt  
 159. *Valoniopsis spiralis* (L.) Rostk Schmidt  
 160. *Callitriche* sp.  
 161. *Utricularia* sp.  
 162. *Hydrocotyle* sp.  
 163. *Salvinia* sp.  
 164. *Wolffia* sp.  
 165. *Elodea canadensis* (Mill.) B. S. P.  
 166. *Hydrilla verticillata* (L.) Rostk Schmidt  
 167. *Valoniopsis spiralis* (L.) Rostk Schmidt  
 168. *Callitriche* sp.  
 169. *Utricularia* sp.  
 170. *Hydrocotyle* sp.  
 171. *Salvinia* sp.  
 172. *Wolffia* sp.  
 173. *Elodea canadensis* (Mill.) B. S. P.  
 174. *Hydrilla verticillata* (L.) Rostk Schmidt  
 175. *Valoniopsis spiralis* (L.) Rostk Schmidt  
 176. *Callitriche* sp.  
 177. *Utricularia* sp.  
 178.

[illegible][illegible]

1. The first part of the document is a letter from the President of the United States to the Congress, dated January 3, 1862. It is a very long letter, and it contains a great deal of information about the state of the country at that time.

clearly defined and there is often considerable overlapping of symptoms and signs. They may indicate the presence of a local tumor caused by a gumma, a transverse myelitis, or an acute or chronic meningitis, while an arteritis leading to aneurysm or occlusion of a cerebral vessel may simulate the vascular accidents of arteriosclerosis, hypertension or a congenital aneurysm, and finally they may be degenerative as represented by general paresis and locomotor ataxia. In order to avoid repetition and confusion, details of syphilitic diseases of the nervous system have been considered in Chapter XV.



Fig. 474.—Syphilitic alopecia showing typical moth eaten appearance of hairy scalp (Courtesy of Dr. John A. Fordyce and Dr. George W. Mackee. From Sullivan and Sutton, Diseases of the Skin.)

### Congenital Syphilis

Syphilis is transmitted to the fetus from the mother and never directly from the father. The mother is most likely to be infected within the first three years after the infection of the consort. As each year passes thereafter this becomes less likely, but the mother may infect the fetus via the placenta for many years after her initial lesion. The more recent the infection in the mother, the more likely is early infection of the fetus to occur. If the fetus be infected early in the pregnancy it usually dies *in utero* and is expelled and there may be several such episodes before a living child is born. On the other

hand, if the mother has been infected ten or more years before conception, miscarriages are not so frequent. A child may be born at any time after the maternal infection exhibiting at birth unmistakable signs of syphilis, or it may be comparatively healthy but a positive Wassermann test will be found in both mother and offspring. In syphilitic children where the signs of infection are not present at birth, these may appear at any time that is within a few months or years, or not until puberty or even later.

In stillborn syphilitic fetuses, or in infants born with signs of syphilis, the Treponema are present in very large numbers in fact there is a spirochetemia. They are particularly numerous in the liver adrenals lungs and the cutaneous lesions. Such infants do not live more than a few days or weeks, and at autopsy there will be found intense syphilitic lesions in the lungs liver adrenals and to a less pronounced degree, in the kidneys and pancreas.

**Symptoms and Signs**—These do not differ materially from those of the secondary stage in acquired syphilis. There are however, certain features which are characteristic such as fissures about the angles of the mouth and in the mucous membranes of the cheeks. There is a nasal discharge commonly called "snuffles." The rashes are both macular and papular and sometimes bullous and are most frequently found on the buttocks and the face. These have a coppery brown color. Syphilitic erythema and eczema are also recognized. The papules or more deeply seated lesions may coalesce particularly on the hands and feet and about the mouth, forming large confluent lesions. Deep infiltration of these on the skin and mucous membranes of the lips may form an indurated mass which is called "cheilitis diffusa" and when the fissures are deep and ulcerated they are called "rhagades." The bullae are the most serious cutaneous lesion and when the superficial covering is removed leave large ulcerating areas. There may be also alopecia and onychia as in adults.

The less distinctive signs and symptoms are retardation of physical and mental development restlessness insomnia and the child may be wakened out of sleep with a high pitched cry or whine. Enlargement of the liver is common and in the spirochetemic cases there is splenomegaly. There may also be a pronounced anemia and a hemorrhagic diathesis which is comparable to that which occurs in all forms of septicemia.

In the years of childhood a characteristic osteochondritis of the centers of ossification of the long bones is sometimes found. Instead of the thin line of calcification it is widened and irregular. This often gives rise to local pain tenderness and swelling. The lower end of the femur is a favorite site. Hutchinsonian teeth are pathognomonic of congenital syphilis. The most obvious deformity is in the central incisors, where a half moon shaped defect on the biting surface is found and these teeth are also frequently peg shaped that is broader at the gum than at the free margin. Karnosh who has made a careful study of the histopathology of these teeth, concludes that the true Hutchinsonian incisor is a deformity of the developmental lobes of the permanent central incisor and not one of transitory calcium deficiency. Another characteristic deformity of the teeth is the mulberry shape of the first permanent molar. Karnosh has shown that this is due to crests of sound

enamel being on a base of hypoplastic deposit. The cusps are generally crowded back on a crown surface of dwarfed dimensions." At puberty there may appear a diffuse hepatitis which may in time progress into cirrhosis of the liver. The lesions of the central nervous system are similar to those in the acquired form. There may be congenital paresis and tabes dorsalis as in the acquired syphilis and this often appears in the first living member of the family and the subsequent ones may escape. Epilepsy and progressive idiocy are not uncommon nor is hydrocephalus which may be suspected as being



Fig. 45.—Photograph of child with congenital syphilis showing characteristic changes about the mouth and on the fingers.

present when the fontanelle remains open and there is venous engorgement on crying or coughing. Other characteristic but less common lesions are syphilitic keratitis, syphilitic otitis and optic neuritis.

**Diagnosis.**—The diagnosis of the primary lesion in acquired syphilis is as a rule made without difficulty. It may be confused with a chancre or soft sore, herpes, lympho-angiomatosis, cutis or inguinalis or a simple traumatic injury. It should not be difficult to differentiate between these as the chancre is so characteristic but it must always be remembered when late syphilitic

signs appear that the site of the original infection may not be detectable. All suspicious sores should be examined for the presence of the Treponema and monthly Wassermann or Kahn reactions should be done for at least six months if there is still any doubt. Shortly after the initial infection there appears in the blood an antibodylike substance closely connected with the gamma globulin fraction of the plasma. It is not yet proved that this is a true antibody. It is therefore called a reagin. This is not the place to discuss the possibilities of a positive reaction indicating some other lesion but if it be repeatedly positive the diagnosis of syphilis should be maintained until such time as the real cause can be ascertained. A greater difficulty in diagnosis is encountered when skin eruptions appear which may simulate some quite benign condition and there is no history of a primary infection. A Wassermann or Kahn test should be done in all such cases. Of still greater difficulty are those that do not give a history of either primary or secondary lesions but seek medical advice for some visceral or nervous complaint. The routine use of a



Fig. 46.—Hunter's syndrome. (Courtesy of Dr. C. R. W. Wende. From Sutton and Sutton, *Diseases of the Skin*.)

Wassermann or Kahn reaction in hospital wards has detected many unsuspected cases of syphilis or has clarified otherwise obscure diagnoses. If syphilis is suspected and the Wassermann reaction is negative the investigation of the case is not complete until a spinal fluid examination has been done. Occasionally where the blood serum reactions may be negative the spinal fluid reactions will be positive. In conclusion as to diagnosis it is a safe rule to suspect all conditions which cannot readily be accounted for by some obvious cause as being syphilitic until this possibility has been proved to the contrary while on the other hand it must not be concluded that every lesion occurring in a person with a positive Wassermann reaction is necessarily syphilitic.

**Course and Prognosis.**—The course of syphilis differs greatly from person to person. In some who are undoubtedly syphilitic neither primary nor secondary signs or symptoms are recorded in the history. The fulminating cases of past generations are now infrequent. Further an individual may have contracted the infection in the twenties and live to be an octogenarian without any evidences of it except a positive serological reaction which may have been found during a routine examination.

Apart from the mortality from congenital syphilis and those who die as a result of the more advanced functional defects of the central nervous system and the cardiovascular system, the death rate is comparatively low. Syphilis can be cured and before serious visceral lesions occur, provided treatment be instituted in the early stages, and be persisted in until a cure can be pronounced.

**Treatment—Prophylaxis**—The best prophylaxis is to avoid promiscuous sexual contact. In the past 25 years active prophylactic treatment has been used extensively. Immediately after exposure thorough cleansing of the genitalia with soap and water followed by a generous and extensive application of calomel ointment has undoubtedly been successful in a large number of cases. This would be expected as the treponema is a particularly fragile organism which is easily killed. Therefore it is of the greatest importance that these prophylactic measures should be carried out within a few hours after exposure before the organism has had an opportunity of penetrating the superficial layers of the skin. Congenital syphilis to a large measure can be prevented by doing a Wassermann, Kahn or other specific diagnostic test on all pregnant women before the fifth month. If positive, proper treatment should be immediately started. This will insure the majority of infants born of such mothers being nonsyphilitic.

**Curative**—The cure of syphilis rests upon two main principles, thoroughness and persistence. In the acute stages, that is during the period of dissemination of the treponema, it is well to keep the patient in bed, particularly if there is pyrexia. At this time he should have a dental examination and thorough oral hygiene should be instituted in preparation for a probable period of mercurial therapy. He should be reassured that cure is not only possible but almost certain, provided he is obedient. The diet and general regime should be that of any infection and after he is allowed to return to his usual occupation fatigue, overwork and worry should be avoided and in other manners he should lead a normal rational life of abstinence and should be encouraged to take outdoor recreation and a sufficient amount of sleep. In married people a difficult situation naturally arises. This is best handled by frankness on both sides and the physician will often be called upon to be the guide, counsellor and friend. It is imperative, however, that any chance of cross infection should be prevented and this can best be accomplished and other complications avoided by knowledge rather than by ignorance. Under present methods of specific therapy a patient can be rendered noninfectious in a matter of a few days.

**Specific**—As soon as the presence of the infection is recognized active treatment should be begun. A few exceptions to this will be dealt with below. If the disease is in the serological negative stage it is improper to wait until the reactions are positive because it is at this phase that the greatest curative success is to be hoped for. Not only will this be more certain of accomplishment but there will also be a fair expectation that neurological and cardiovascular syphilitic lesions will be prevented. At one time it was considered proper to carry on the treatment in periodic courses. It is now the consensus of opinion that it is much better for the treatment to be con-



tinuous. This applies where arsenic alone is used, and also where it is alternated with or supplemented by, mercury, bismuth penicillin or chloromycetin.

The treatment has rested upon the use of arsenic in the form of neoarsphenamine, arsenoxide (mapharsen), the heavy metals, bismuth and mercury, penicillin and chloromycetin and potassium iodide. The first five are direct treponemacides, while the last although having no direct action upon the treponema is of value in promoting the absorption of syphilitic exudate and scar tissue. There are a number of other arsenical preparations now in vogue—sulfarsphenamine, tryparsamide, etc. They each have virtues but are best employed by those who are expert in the treatment of syphilis or have adopted this branch of medicine as a specialty. Neoarsphenamine is probably the better arsphenamine as it can be more easily prepared, but on the other hand, it is less constant in its toxicity and somewhat less effective. Sulfarsphenamine is used considerably in pediatric practice as in children the intramuscular administration is seldom followed by severe local reactions. Mercury, a drug of ancient and honorable reputation is being replaced by bismuth. It may be administered either by mouth byunctions or by intramuscular injection of one of the soluble salts such as the bichloride, cyanide, oxycyanide or succinimide, or in insoluble salts such as mercury salicylate suspended in oil may be given intramuscularly. This has a disadvantage of being painful and often gives rise to severe local reactions.

Bismuth has become a favorite heavy metal in the treatment of syphilis. It is given intramuscularly as a salt such as sodium potassium bismuth tartrate or bismuth subsalicylate. The doses of these various chemical treponemacides are given in Table XIX.

TABLE XIX

ARSENICALS	BISMUTH	MERCURIAL
<i>Intravenously</i>	<i>Intramuscularly</i>	<i>By Mouth</i> three times a day
Arsphenamine weekly 0.2 to 0.6 gram	Bismuth subsalicylate in oil 0.2 gram weekly	Mercury bichloride $\frac{1}{2}$ grain
Neoarsphenamine weekly 0.6 to 0.9 gram	Na K bismuth tartrate 0.1 to 0.2 gram 3 times a week	Protiodide $\frac{1}{2}$ grain
Sulfarsphenamine weekly 0 to 0.6 gram		Metallic mercury (Blue Pills) 1 grain
Tryparsamide 0.5 to 3.0 grams 1 to 2 weeks		Hydragyn perchloride (Green Mixture) $\frac{1}{2}$ grain
Arsenoxide (mapharsen) twice weekly 0.04 to 0.06 gram		<i>Intramuscularly</i> 1 to 2 days apart
		Bichloride Cyanide Oxycyanide Succinimide 0.01 gram
		<i>Intramuscularly</i> weekly
		Mercuric salicylate 0.2 gram weekly
		<i>Inunction</i> daily
		Metallic mercury (Blue Mass) 1 dram

Penicillin has been found to be an excellent agent in the treatment of this disease. It has been given in amounts of 30,000 to 90,000 Oxford units every three hours until 2 to 5 million units have been given. It is well to combine it with arsenicals and bismuth. It is strongly indicated when the possibility of reactions or hepatic or renal damage is to be avoided as in pregnancy.

Potassium iodide in amounts of 10 to 40 grains, three times a day, may be given continuously. There is no reason to omit it even in the earliest cases, and in the older lesions it is often wise to institute a preliminary intensive course of iodide before the treponemacides are started. It should always be administered with large amounts of water.

At the beginning of the treatment the full doses of the chemical and anti-biotic treponemacides should not be given but should be started at about one third the usual amount and be gradually increased up to the maximum.

The chemical treponemacides are all toxic drugs. Although they may have a selective action on these organisms, they are not without effect upon the fixed cells of the body. There are certain effects or reactions which should be avoided. These are as follows:

**Arsenicals**—1 *Nitritoid Crisis*—During the administration of an arsenical preparation flushing, tingling of the skin of face, neck, and extremities, with injection of the conjunctiva may be complained of. This is immediately followed by a sense of suffocation and choking, palpitation, and sometimes edema of the lips and face. There may be collapse. These symptoms closely simulate an anaphylactic shock, and have been attributed either to an idiosyncrasy on the part of the patient to this particular arsenical preparation or to faulty technique. As it is apt to recur on each succeeding injection it seems more likely to be due to the former. It is best treated by 10 minims of adrenalin subcutaneously.

2 *Dermatitis*—The patient should be cautioned to inform his physician if there is any itching of the skin during the course of treatment, as this is the first indication of the onset of an exfoliative dermatitis which may be quite serious not only on its own account but also because it requires a discontinuance of all arsenical preparations and further prevents the use of mercury in the form ofunctions.

3 *Jarisch Herzheimer Reaction*—This is characterized by symptoms referable to the central nervous system and seems to be connected with a sudden destruction of the treponema with syphilitic intoxication as there is a temporary aggravation of the symptoms of the disease. It may occur when the principal syphilitic manifestations are in any site. It usually follows after the first dose in twenty four to forty eight hours. It is most frequent in chronic cases and in these the amount of the initial injection should be about one quarter of the average dose. It is relatively uncommon in lesions of the nervous system but more common in those of the skin, liver, and heart. The time interval varies considerably. In the nervous system it usually does not occur until the second to fourteenth day. After tryparsamide, it is as a rule delayed until the second or third week.

4 *Hepatitis*—In some cases arsenic seems to have a particularly toxic effect upon the liver. Therefore the slightest suggestion of jaundice indicates the discontinuance of the drug. In suspicious cases or in those with a history of jaundice or hepatic disturbances it is well to check this matter by the van den Bergh reaction done at regular times.

■ *Aplastic Anemia*—Arsenic has at times what appears to be a specifically toxic action upon the bone marrow, and may lead to a rapid anemia of the aplastic type. It is sometimes difficult to be certain whether the intoxication of the bone marrow and the anemia are due to the action of the arsenic or the treponema.

6 *Agranulocytosis*—An increasing number of cases are found in the literature where agranulocytosis (see page 564), particularly in women develops during or following the administration of arsenic. The connection between these two events is not always clear, but there are sufficient cases reported in which there seems to be a definite connection rather than a coincidence, to warrant sounding a word of warning in this regard.

7 *Sudden Death*—This sometimes occurs particularly in long standing cardiovascular and cerebrospinal syphilis in association with some of these reactions but there are other instances where it cannot be accounted for by any of them.

■ *Blindness*—Serious visual damage may result from the use of tryparamide. This drug should never be given to patients with preexisting optic atrophy. Before starting treatment examination of the fundi visual acuity and visual fields should be carried out. The slightest subjective or objective evidence of visual disturbance calls for immediate cessation of treatment.

*Mercury and Bismuth*—These are apt to produce salivation, stomatitis, diarrhea and nephritis. Therefore strict oral hygiene should be insisted upon and the urine examined weekly while these drugs are being given.

*Penicillin*—The toxic reactions are comparatively insignificant and consist of urticaria, dermatographism and a clinical picture like serum sickness. It must be appreciated that it may produce a Jarisch Herxheimer reaction.

The treatment of early syphilis has been a fruitful field in therapeutics and this has been made somewhat more complicated by the introduction of penicillin and chloromycetin as powerful antisypilitic agents. For a time there was considerable controversy waged around the intensity and duration of arseno therapy. Short courses with high dosage versus longer periods with smaller doses divided the profession. Further there was a difference of opinion as to the time and place for mercury and bismuth. Now penicillin and chloromycetin have entered the field. In fact the successful treatment of this disease requires such constant vigilance and thorough knowledge of the variations, indications and complications which are inherent in the use of these drugs and in the disease itself that it is claimed by many that it should be left in the hands of those who specialize in this disease. There is no doubt that they obtain a much higher percentage of cures as compared to those who treat a case occasionally. It could be compared to the treatment of tuberculosis. In both the early diagnosis is the responsibility of the general physician the treatment that of the specialist.

In latent or late syphilis the interval between the time of the original infection and the time the patient comes under observation to some extent determines the line of action. If many years have passed (the patient being over sixty five years of age) and there are absolutely no signs of functional or anatomical changes which can be attributed to the syphilitic infection a positive Wassermann may be ignored. The other cases should be treated more

along prophylactic lines for the prevention of syphilitic activity than with the hope of completely eradicating the infection. The therapy may be less heroic and persistent periodic courses of neoarsphenamine and mercury or antibiotics being given at intervals of a few months. The urine should be frequently examined for albuminuria and constant vigilance maintained for the appearance of the slightest jaundice. Potassium iodide ought to be given continuously. In chronic bone lesions without cardiovascular or cerebrospinal involvement the treatment is similar to the acute cases.

Cardiovascular syphilis occurs in inverse ratio to the institution of early treatment and is found in about 10 per cent of all syphilitics, being twice as common in males as in females. It is interesting, however, that only about 50 per cent of these cases give a history of a primary infection and one third have complicating neurovascular syphilis. Particular caution should be exercised in the treatment of these cases as it is not infrequent for sudden death presumably due to ventricular fibrillation or a Herxheimer reaction to occur or a therapeutic paradox may develop. This term is used when there is a rapid depreciation of cardiovascular function or acute congestive failure shortly after antisyphilitic treatment has been started. It follows the use of arsphenamine. Therefore the drugs best suited for treating these cases are mercury bismuth iodide in small doses, penicillin and neoarsphenamine. Either of the heavy metals may be combined with arsenic which is best given as neoarsphenamine in doses not greater than 0.1 gm per week but should be continued over long periods. Aneurysm, aortic insufficiency, or chronic circulatory failure are not influenced by the antiluetic treatment and all have a serious prognostic significance. If precordial pain (angina pectoris) is present antiluetic treatment must be used with great caution. Arsenic is contraindicated in hepatic syphilis.

The treatment of neurovascular and meningovascular syphilis has been dealt with under Diseases of the Nervous System (see page 1063).

The treatment of congenital syphilis in no way differs from that used in adults. The mercury may be smeared over the abdomen under a binder or given in the form of grey powder  $\frac{1}{2}$  grain three times daily. Infants seem particularly tolerant of sulfarsphenamine which may be given in doses appropriate to the age of the patient (see Chapter XIV).

## YAWS

**Synonyms**—Frambesia pian boubia

**Definition**—Yaws is a specific infection which runs a chronic and recurrent course. It is caused by a treponema closely allied to that of syphilis. In fact many were formerly of the opinion that these two diseases were due to the same cause but were different manifestations changed by local geographical influences and different reactions of the host. Yaws is now considered to be due to the *Treponema pertenue* first described by Castellani. It is found in the tropics of Asia, Africa, Australia and America. It is not a venereal disease although it is transmitted by direct contact.

**Symptoms and Signs**—The incubation period is two to four weeks. The portal of entry is through the skin, and the *primary lesion* is usually on the breast or buttock in women and the extremities in men and children. The exact reason for this distribution is not clear. This lesion is called the 'mother yaw,' 'mamam pirn,' or 'boubi midre.' It begins as a papule and at the end of about one week it acquires a moist surface with a yellow secretion and a dry crust. It may be multiple and coalesce, forming larger lesions. When the crust is removed there is found a clear cut ulcer with a granulating base.

The primary lesion is accompanied by general malaise, low irregular pyrexia, headache and general muscular pains. The neighboring lymph glands soon become large and hard but do not break down. The primary lesion is indolent but eventually may heal or become a large granulating mass. The general symptoms usually disappear temporarily. The *secondary lesions* indicative of a general dissemination of the spirochete appear in about five to twelve weeks after the primary lesion. There is now a recrudescence of the general symptoms, the pains in the muscles, joints and bones, and headache being especially severe. Small reddish papules appear in the skin. They are widely distributed and persist for many weeks. Some gradually disappear, others coalesce to form large areas with an areola darker in colored races and reddish in white races.



Fig. 4.—Typical yaw, tertiary stage showing one rather unusual bone lesion. (Courtesy of Drs. C. L. Sackett and Leta M. Sackett. From Sutton and Sutton: Diseases of the Skin.)

In the tertiary stage there are deep seated gummatous nodules in any tissue but chiefly in the bones and muscles. The *boomerang shin* of the Australian aborigines is held to be due to yaws and is analagous to the sabre shin of syphilis. The viscera are not involved. In the skin the nodules ulcerate and may be extensively destructive. Secondary epithelioma in untreated cases is common.

**Pathological Anatomy**—The pathological anatomy is essentially granulomatous particularly in the secondary stage when there is great thickening of the skin. In the tertiary stage the destructive qualities are the most distinctive.

**Diagnosis**—The diagnosis is seldom difficult in endemic areas. The treponemata can be readily found by methods similar to those used in syphilis. The Wassermann reaction is positive so that the differential diagnosis is made on clinical grounds alone, as there is no microscopical or serological test to differentiate syphilis from yaws.

**Course**—The course of the disease is protracted, but it does not kill as a rule, although death may be due to secondary infection through the secondary or tertiary cutaneous lesions. It is more disabling than fatal.

**Treatment**—The treatment is similar to that for syphilis. Neosarsphenamine first dose 0.3 gram, subsequent ones 0.6 gram with three to five days'



FIG 478.—Lues in a young Siamese. (Courtesy of Dr Ralph Mendelson. From Sutton and Sutton, Diseases of the Skin.)

intervals for six to eight doses is efficacious. Stovarsol, one gram daily, in divided doses by mouth also gives good results. Pemeillin would appear now to be replacing the arsenicals in the treatment of this disease. It is administered after the same manner as for syphilis but the amounts required are

much less and the duration of the treatment is shorter, as follows 1 200 000 O U in thirty divided intramuscular doses at three hour intervals or 1 200 000 O U in oil with beeswax intramuscularly in two doses at 24 hour intervals Potassium iodide is to be advocated particularly for the granulomatous lesions By these measures cure is usually assured

### LYMPHOPATHIA VENEREUM

**Synonyms**—Benign lymphogranulomatosis, paradenitis climatic bubo Nicolas Favre disease lymphogranuloma inguinale

**Definition**—Lymphopathia venereum is a specific infectious disease It is transmitted by venereal contact and the portal of entry is an inconspicuous primary lesion followed by lymphadenitis suppuration and cicatricial deformities

**Etiology**—The cause of the disease is a filtrable virus The pus from the lesions contain elementary bodies similar to those found in psittacosis The disease has been experimentally induced in mice, guinea pigs and monkeys

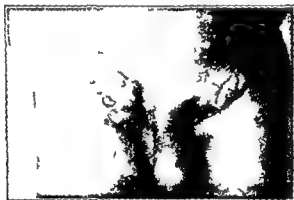


Fig 49—Classical lymphogranuloma inguinale. Frei test positive (Courtesy of Dr Harold N Cole) (From Sutton and Sutton Diseases of the Skin)

**Symptoms and Signs**—The disease is transmitted by sexual contact and so is called the 'fourth venereal disease' It may, however be contracted by extragenital routes especially through the mouth The incubation period is variable—one to seven weeks, averaging about three weeks The initial or primary lesion is usually an inconspicuous single papular infiltration on the glans penis or prepuce in the male It seldom appears on the vulva in the female but when recognized is found on the fourchette It is probably more common within the vagina which may account for the variations in glandular involvement in the two sexes Occasionally the primary lesion may be vesicular or herpetic with erosion while in others it may simulate the chancre of syphilis but is softer and more superficial This primary stage may be accompanied by slight pyrexia malaise headache and anorexia

After two to three weeks the glands in one groin (rarely bilateral) enlarge and become painful At first discrete they soon merge into a large mass The skin soon becomes attached and appears purplish or dark red with signs of

**Course**—The course of the disease is protracted, but it does not kill in a rule, although death may be due to secondary infection through the secondary or tertiary cutaneous lesions. It is more disabling than fatal.

**Treatment**—The treatment is similar to that for syphilis. Neosarsphenamine, first dose 0.3 gram, subsequent ones 0.6 gram with three to five days'



Fig. 478.—Yaws in a young Siamese. (Courtesy of Dr. Ralph Mendelson. From Sutton and Diseases of the Skin.)

intervals for six to eight doses is efficacious. Stovarsol, one gram daily, in divided doses by mouth also gives good results. Penicillin would appear now to be replacing the arsenicals in the treatment of this disease. It is administered after the same manner as for syphilis but the amounts required are



ifestation of cutaneous leishmaniasis (oriental sore, see page 710) and is mentioned here to draw attention to its distinction from the previous disease. The treatment is by antimony salts intravenously given in the form of ammonium antimony tartarate.

## GONORRHEA

### Synonym.—Clap

**Definition**—Gonorrhea is an acute and chronic infectious disease caused by the gonococcus. It is most commonly a venereal disease although not necessarily so. The infection may remain comparatively local or become systemic.

**Etiology**—It is due to the gonococcus which is biscuit shaped gram negative intra and extracellular diplococcus. It will not grow on ordinary artificial media but requires special preparations such as meat, peptone brain agar, or those that contain aseptic fluid or fresh blood. It also grows best when exposed to a low partial pressure of oxygen. There seems to be a variability in virulence in different strains. It is contracted usually through sexual intercourse with an infected person. Occasionally in newborn infants the eyes may be infected, and young girls may contract it through extrasexual contact with infected towels, clothing and bed linen. Boys are seldom so infected.

**Symptoms and Signs**—The incubation period is usually four to five days. The portal of entry is through the urethra in the male, and the urethra and vagina in the female. There is a profuse urethral or vaginal purulent discharge. Therefore the local symptoms differ somewhat in the male and female.

Gonorrhea in the male may cause so little discomfort as to pass unnoticed by the patient who has heard so much concerning the severity of the symptoms. On the other hand the urethral inflammation may be severe, the discharge thick and profuse and surrounding penile structures may be so affected as to produce irregular and persistent distention which is exquisitely painful causing penile curvature on erection (chordee). If the infection proceeds into the membranous urethra bladder symptoms—frequency, urgency, dysuria and tenesmus—may be severe and on micturition there may be a terminal hematuria. Invasion of neighboring structures may occur producing cystitis, prostatitis with abscess, epididymitis, orchitis, infected phimosis and paraphimosis, balanoposthitis, Cowper's abscess and parafoveal abscesses. When the urethritis is severe or any of these adjacent tissues or the posterior urethra are involved a systemic reaction may occur. There is general malaise, pyrexia and leucocytosis but unless there is a systemic infection or a local retention or abscess these are of mild degree. The disease may be prolonged and develop into a chronic state. This is invariably due to some focus in the adjacent structures which is not draining properly and remains infected. This is not only important in the perpetuation of the local condition but also as a source for hematogenous or metastatic spread of the virus. Stricture of the urethra occurs at times due to local ulceration and loss of substance with scar formation.

Gonorrhea in the female affects the urethra but symptoms referred to this structure are not as pronounced as in the male. There may be no urethral symptoms whatever. When present there is burning and some pain on urination. The

peradenitis and then isolated points of softening appear which rupture, producing multiple sinuses discharging a thin seropurulent fluid. In women the same sequence of events occurs but the pelvic and perirectal glands are more commonly affected. The true nature may not be recognized although there may be a discharge from the rectum and painful defecation.

In distinction to the mild systemic symptoms of onset there develop with the adenitis in most cases a pronounced pyrexia, sometimes as high as 104°F, and prostration. There may also be delirium, semi-coma and signs of dehydration. The pulse is always slow. The liver and spleen are enlarged and there is usually a mild general adenopathy. An arthritis has also been reported in a fair number of cases. There are a slight anemia and a leucocytosis, with frequently a mononucleosis. An interesting laboratory finding is a hypoglobulinemia.

Cases vary considerably in the intensity of the systemic reaction but in all the adenitis passes into a chronic course of many weeks, months, or even years duration. Eventually there is healing with massive and destructive scarring which may lead to rectal stenosis and elephantiasis of the penis and scrotum in the male and vulva and perineal regions in the female.

In the rare cases where the portal of entry is through the mouth, the tonsils and cervical glands (unilateral) follow the same course.

**Pathological Anatomy**—The anatomical picture is that of an infectious granuloma with suppurative adenitis and peradenitis. There are no specific histological characteristics. With healing dense scar tissue produces distortion and lymphatic obstruction.

**Diagnosis**—This disease has to be distinguished from syphilis, chancroids, gonorrhea, bubonic plague, and other causes of suppurative adenitis. This is usually not difficult if the possibility of its occurrence be kept in mind. Where as it was at one time considered to be a tropical and semi-tropical disease it is now known to have a wide distribution and is yearly being reported from new districts. The diagnosis can be established by the Frei test for cutaneous sensitivity which becomes positive at the time the adenitis first appears. It must also be differentiated from granuloma inguinale in which, however, there is no adenitis.

**Prognosis**—As mentioned above the course is essentially chronic, while the morbidity is great the mortality is low.

**Treatment**—There is no specific cure and perhaps the best procedure is surgical removal of the involved glands before they suppurate. On the other hand increasingly good results are being reported with potassium antimony tartrate. This is used in the same manner as in schistosomiasis (see page 710). It is most efficacious before suppuration but should also be used even under these conditions. Sulfadiazine should also be given (1 gram every 4 hours) in full doses. There is little evidence that it affects the virus but rather secondary infections.

### GRANULOMA INGUINALE

Granuloma inguinale is an infectious disease of the genitalia particularly of the pudenda. It is caused by *Trichomonas tropica*. The lesion is a local one

arthritis the intensity of the pain and tenderness causes the patient to prevent all movement, and fixation in these faulty positions rapidly occurs. Suppuration and erosion of the cartilage with destruction of the articulating surfaces sometimes occur and the infection may be so intense as to lead to perforation of the joint capsule with involvement of the skin causing a sinus. The periarticular tissues (tendon sheaths and tendons) may be also involved independently of the joint but with perforation of the joint capsule infiltration of the periarticular tissues and the contiguous structures may lead to more extensive local incapacity and joint fixation. It is during this period that the surgeon sees the case in order that the suppurating joint may be drained. This should be delayed as long as possible as what may seem like a purulent destructive lesion makes a remarkable recovery although there may be some distortion. The chronic fixed deformities are those seen by the orthopedic surgeon, but even in these it is surprising what a good result may be obtained by gently breaking down adhesions under an anesthetic and putting the joint in a proper position. If this manipulation is delayed too long fixed fibrous and even bony ankylosis may result from this neglect.

The ophthalmia which is caused by the gonococcus may be by direct contact of the conjunctiva during birth through an infected canal. This, however, comprises but a small percentage of the ophthalmic cases. Many others result from metastatic infections via the blood stream in the same manner as gonorrheal arthritis. These cases chiefly cause an iridocyclitis as well as a conjunctivitis and in some panophthalmitis may ensue. They are not common but are destructive and simulate the ocular lesions of tularemia.

The endocardium (see page 413) has been reported by Thayer to be the site of ulcerative endocarditis in 7 per cent of such infections. This is undoubtedly too high as his cases were largely drawn from a population with a high percentage of gonococcal infection. The average incidence is probably about 3 per cent of cases of ulcerative endocarditis. This condition has been dealt with elsewhere.

The skin lesions are of two kinds namely the local condylomata acuminata which are small papillary growths upon the external genitalia in women which are bathed in the copious and irritating gonococcal discharge from the urethra and vagina. They are principally the result of lack of cleanliness. The other dermatological manifestations are due to a systemic spread of the virus. They may occur with or without an endocardial lesion. There have been described erythemas and erythema nodosum which are not particularly characteristic of this infection. There are however certain hemorrhagic and bullous pustular eruptions which are quite suggestive. They are undoubtedly embolic and closely simulate the severe skin manifestations of meningococcal infections. But almost specific are the lesions with hyperkeratosis. They are supposed to be rare but undoubtedly they are often overlooked. They may be associated with or follow an arthritis. As they are due to a bacteremia this is to be expected. They suddenly appear on the palms of the hands soles of the feet and about the nails. There are scaly efflorescences with little or no reaction but the whole cutaneous sole palm or nails may be separated

meatus is reddened and pouting and exudes a thick yellow pus. On palpation through the vagina it is tender, and may be felt as a firm band beneath the vaginal mucous membrane. The inflammation may extend to the bladder and cause cystitis with frequency and urgency. The discharge from the urethra rapidly diminishes until it may disappear except when the urethra is milked a small quantity of pus may be expressed. As in the male, a chronic urethritis is common but it rarely leads to stricture.

Although the vagina may contain considerable pus it is seldom actively involved, as the vaginal epithelium is resistant to the organism. The cervical canal is, however, a common site for a severe and resistant infection, and from here there is a creamy leucorrheal discharge. Skene's and Bartholin's glands are also common sources of persistent infection and an abscess or a cyst may be formed. The bladder, endometrium, endosalpinx, ovaries, pelvic peritoneum, and pelvic tissues may be involved. Gonorrhea is the most common cause of chronic inflammations of the female pelvic organs, and an equally important cause of sterility. The symptoms apart from a leucorrhea are vague but persistent. There is pelvic pain, low back pain and general debility, while locally the pelvic organs are fixed and painful on examination. An acute infection usually reveals the acute inflammatory reaction already described but the chronic infections are less distinctive and often require careful and expert examination to prove their identity.

Systemic infection by the gonococcus is relatively uncommon, but when it occurs it is serious. As in syphilis the inguinal glands may become enlarged and suppurate, causing a bubo which may ulcerate through the skin and cause a sinus. The gonococci may, however, pass through these glands without producing a local adenitis. A general infection usually occurs during the period of acute genitourinary infection but not necessarily so. In fact metastatic lesions may develop with little or no evidence of persisting local disease. The gonococcus has a particular selective action on the synovial membranes of the joints and tendon sheaths, the eye, the endocardium and the skin.

Gonorrheal arthritis is the most common lesion resulting from a systemic infection. It usually is polyarthritic affecting principally the larger joints. At one time it was considered that it differed from rheumatic fever in that the arthritis was not fleeting in distribution. This is quite an erroneous conception having arisen from the fact that minor pains and aches with some swelling may be so transitory as to pass unnoticed, particularly if one or more joints are severely involved. After the general arthritis has persisted for a few days, there may be pronounced swelling of one or several of the larger joints with redness, intense pain, fluctuation, and characteristically, exquisite tenderness. The patient often cries out with pain even when the bed is approached, the bedclothes touched, and of course when the limb is moved. The emotional disturbances are more extreme than would be expected and are characteristic of this infection. The limb is held in a position of semiflexion when the knee or elbow is affected, the foot is extended when the ankle is involved and the leg is rotated outward and fixed when the hip is involved. These are the positions usually assumed in any arthritis of these joints but in gonorrheal

ovaries and pelvic cellular tissues. The gonococci may not be demonstrable, but with alcoholic or sexual excesses a recrudescence may occur. It is therefore prudent not to be too certain of a cure and the patient should be duly impressed with the seriousness of the condition. Gonorrheal arthritis usually completely recovers without permanent disability, although there is no doubt that some cases are eventually classified as arthritis deformans. Endocarditis is often fatal. The ocular lesions may cause permanent disabilities and are a common cause of blindness.

**Treatment—Prophylaxis**—There is no true immunity to the gonococcus but the infection may be prevented if certain precautions are taken. The first is obviously the avoidance of sexual connection with infected persons. Secondly, if it must be then prophylactic measures should be promptly used.

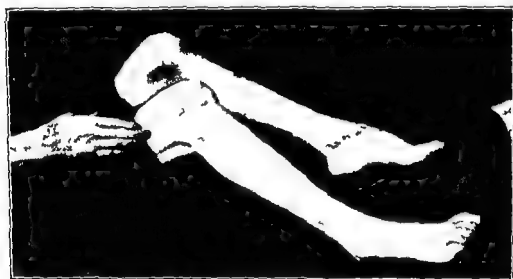


Fig 450—Photograph of a case of gonorrheal arthritis and of gonorrheal hyperkeratosis of the feet and feet.

These consist of thorough washing of the external genital parts with soap and water and the injection into the urethra of 5 cc of 10 per cent argyrol or other selected antiseptic which should be retained for five minutes. This should be done as soon as possible but even up to twenty four hours it has been known to be effective. This should be followed by a generous application to the external genitals of 30 per cent calomel ointment to prevent syphilis. The prophylactic use of sulfadiazine has had a considerable vogue. There is evidence that it is somewhat successful but if used constantly there is also evidence that resistant strain of the organism develop.

**Active Treatment**—There is probably no disease where more harm has been done by rough methods of so called cure as in gonorrhea. This organism can only penetrate the more delicate epithelial coverings and anything which injures these promotes further extension of the infection. Therefore the local treatment should be gentle and not directed toward actual disinfection but rather local removal of the exudate. The best treatment is local and general.

and beneath leave denuded surfaces which lead to additional keratosis. It is not analogous to a syphilitic lesion, as there is undermining and massive partial separation.

The other metastatic lesions are comparatively rare and it is inconclusive whether they are due to the gonococcus or secondary infections. There may be pneumonia, pleurisy, albuminuria, polyneuritis, meningomyelitis, neuritis and myositis. The local bone lesions associated or not with arthritis form an interesting group, namely, osteitis, periostitis, chondritis and perichondritis, and have been connected with gonococcal infections. In fact the gonococcus as an hematogenous infection may produce a most diverse collection of lesions.

In addition there may be distant local lesions in the anus and rectum, particularly in women. The anal lesions are of little importance except for fissures, while a proctitis may vary from a mild catarrh to severe edema, ulceration and tissue necrosis leading to rectal stenosis.

**Pathological Anatomy**—It is characteristic of the gonococcus that it flourishes best in tissues covered by columnar epithelium. In the primary infection it invades the intracellular spaces and there produces a powerful endotoxin when it disintegrates. There is a great infiltration of leucocytes into the tissues which leads to a desquamation of the epithelium. There may be destruction of tissue, and fibrosis in the genitourinary tract. In the joints the suppuration and necrosis may be excessive, and in the endocardium there is also great destruction of tissue with exudative polypi.

**Diagnosis**—The diagnosis of the local urethral or genital lesion rests upon the well known primary symptoms and the demonstration of the gonococci. This may require most meticulous examination before a definite diagnosis is made and if there be any doubt a specialist's opinion may be necessary. In the acute attacks in the male this is seldom required. In the female diagnosis may not be so easy particularly as the acute external signs are often transitory. In the more chronic cases a thorough and careful examination is necessary. In the male careful massage of the prostate and urethra after preliminary superficial washing may reveal a small amount of exudate in which pus and intracellular gram negative biscuit shaped diplococcus may be found. This is strongly suggestive but not absolute unless the organisms are grown on artificial media. In women chronic gonorrhea is more difficult of diagnosis as the pelvic lesions may result from postpartum infection. In the nulliparous these are however practically pathognomonic. The gonococcal fixation test if positive is indicative that this infection has occurred in the past but does not necessarily render an absolute verdict unless the other clinical findings would indicate it.

The diagnosis of the systemic or metastatic lesions depends upon a careful analysis of all the clinical facts available substantiated by bacteriological and serological evidence. There is probably no infection where the local findings have such a diagnostic significance.

**Prognosis**—The eventual result depends upon an early diagnosis and prompt treatment. The acute urethritis can usually be cured within a few days. But there is a residue of cases that progress to chronic and indolent infection of the prostate, urethral glands, seminal vesicles, the endometrium,

**Etiology**—The *Bacterium tularensense* or *Pasteurella tularensis* is a short aerobic, nonmotile bacillus which stains gram negative. It does not form spores, and in old cultures many coccoid forms may be found. It grows best in media containing 0.1 per cent cystin. The disease has been reported in nearly every state in the Union and a few scattered areas in Canada. It occurs equally in both sexes although men, as will be seen, are more prone to be infected than women and both more than children. Negroes are less susceptible to infection than whites.

**Method of Transmission**—It is spread from one rodent to another by the *Chrysops discalis* which is a biting insect with a wide distribution. Other mites, ticks, lice, etc., which are parasitic to these animals also play a part in its transmission from animal to animal, and they can transmit the infection to man if they attack him. The bedbug also has been accused as a vector.



Fig. 481.—Illustration of the disease, involving right index finger, after repeated ulcerations. Nodular lymphangitis of rising metacarpophalangeal articulation. Photograph taken 12 weeks after onset. (Courtesy of Doctor Walter M. Camp on "Diseases of the Skin.")

There is a different prevalence for the transmission of the disease to man in different parts of the country. In those parts where men are exposed to bites of ticks this is a fairly frequent method of transmission. But the most common manner of infection in man is direct inoculation through the skin in those employed in skinning or dressing rabbits. In the West the jack rabbit is most responsible, while in the East it is the cottontail. Those working in laboratories with this organism are also frequently infected and it has been contracted by those dressing wounds so infected.

**Symptoms and Signs**—The incubation period is one to seven days the average being three and a half days after exposure. The onset is sudden with a chill and pyrexia with prostration, general pains, malaise and headache and the other signs of an acute infection.

rest with a diet free from urinary irritants such as coffee, tea, meat extracts condiments, alcohol, and irritating drugs. Copious fluid intake, simple diet and continence are imperative.

There is no specific serum therapy for this infection. Sulfathiazole and sulfadiazine (Chapter XX) have been advocated for both the primary and the secondary lesions. In regard to the arthritis and ophthalmic lesions the results with sulfadiazine continue to be most encouraging while penicillin has given results in both acute and sulfa resistant cases that are almost phenomenal (see Chapter XX). Conservative and symptomatic treatment must not be neglected. In arthritis, the joints most affected should be kept in an optimum position and when the acute infection has subsided adhesions should be broken down under an anesthetic. This may produce a secondary reaction which should then be allowed to subside also. In a fortnight passive movement should be instituted and gradually active movements. In the meantime local applications of heat and proper splinting to avoid strain and subluxation must be undertaken to prevent deformities. Careful manipulations without trauma are usually successful in producing a thoroughly useful joint even in severe local infections. Hyperthermia therapy by well controlled methods is an important aid in all forms of gonococcal infection and until recently was the only hope in the treatment of the chronic forms but penicillin would seem to supplant this laborious method.

Gonococcal endocarditis was at one time considered incurable. But cases are now being reported as cured with penicillin alone or in combination with sulfadiazine. Ophthalmic lesions should be cared for by an oculist as more harm than good results from improper measures, and each case is a law unto itself. At first instillation of 5 per cent argyrol or other mild antiseptic or irrigant may control the condition, but it must be remembered that the lesion is more often hematogenic than due to direct infection. Therefore external therapy except hot or cold applications is usually of no avail. Foreign protein shock, particularly with milk proteins, has given good results. This brings up the question of such therapy and specific vaccines for the other gonococcal lesions. There is no doubt that good polyvalent or autogenous vaccines when used in a proper manner give encouraging results. General reactions should not be produced as these have a broader effect than for the immediate lesion. Their use is an open question among most specialists. The chronic pelvic lesions in both the male and female are really in the realm of urologists and gynecologists, and rough interference and therapy often do more harm than good. There are two important points which should always be impressed upon the patient, namely, absolute abstinence from alcohol and sexual intercourse until all signs of infection have been absent for some months.

## TULAREMIA

**Synonym**—Ohara's disease

**Definition**—Tularemia is an acute specific infectious disease due to the *Bacterium tularense* which is transmitted to man usually from rabbits or from ground squirrels, mice or other rodents. There is a characteristic primary cutaneous lesion with enlargement of the neighboring lymph glands.



carditis and peritonitis. Meningitis has also been reported. Increasing numbers of cases of lobar pneumonia, bronchopneumonia and bronchitis are being recognized not as primary infections but secondary to the cutaneous lesions.

**Diagnosis**—In a typical case there is little difficulty as the characteristic ulcer and regional adenopathy are so distinctive. A chancre on the finger with enlarged epitrochlear glands may simulate it but should be easily differentiated both clinically and serologically. The most trouble in diagnosis occurs in the small number of cases where the primary sore has not appeared or has been overlooked. The so-called typhoid type must be differentiated from typhoid fever, paratyphoid fever, military tuberculosis and malaria while the glandular type may imitate Hodgkin's disease, infectious mononucleosis or acute lymphatic leucemia. The bacteriological and serological examination of the blood absolutely confirms the diagnosis. Agglutinins in high titer appear early in the disease. The only precaution to be remembered is that occasionally there is cross agglutination with *B. abortus* and *B. melitensis*. An intradermal test is now available.

**Course**—The course of the disease is irregular, the pyrexia usually lasting from three to four weeks. The immediate prognosis is good, the mortality being on the whole under 5 per cent, although in small series it has been reported as high as 15 per cent. The convalescence is tedious as there is considerable physical and mental depression for many weeks or even months.

**Treatment**—Prophylaxis among those who handle rabbits in infected areas is of the utmost importance. It is during the dressing of these animals for food either in the home or for consumption in the general market, or when skinning them for the fur market that many are infected. This is prevented by wearing gloves. In areas where infected ticks and other biting insects which are vectors abound the problem is more difficult. In laboratory workers even the utmost precautions are sometimes of no avail.

The patient should be treated along symptomatic lines as in all acute infectious diseases. The sulfonamides and penicillin have been used with indifferent success but the results with streptomycin are most encouraging (see Chapter XX). This has been used both intramuscularly and by local application particularly in eye lesions. Excellent results would also seem to be obtained by the use of bismuth sodium tartrate intravenously (2 per cent solution). Oxygen therapy may be indicated when pneumonia is present and suppurative pleurisy and peritonitis may require operative interference. The glands should never be incised if it can be avoided. A suppurating gland should be left alone as long as possible with the hope that the general infection will subside before incision is absolutely necessary.

## ANTHRAX

**Synonyms**—Wool sorter's disease, malignant pustule, charbon, milzbrand.

**Definition**—Anthrax is a specific acute infectious disease transmitted to man by direct contagion through the skin and mucous membrane.

**Etiology**—It is caused by *B. anthracis*, which is a rather large gram positive, nonmotile bacillus which grows readily in heaped up bunches of filaments on solid media. The growth has been likened to 'doll's hair'. It was

The primary lesion is most frequently found on the hands or fingers. This is a shallow ulcer which is covered with a greyish membrane, and exudate is not abundant. It is indolent in healing. The virus apparently proceeds from the primary sore via the lymphatics to the lymph glands which rapidly become enlarged and painful. Their size is greater than would be expected and draining into and connecting them reddish purple lymphatic channels are visible. This reaction may be so intense as to cause a widespread lymphangitis. Occasionally cellulitis and suppurative adenitis occur. Although the first regional glands as the epitrochlear are most enlarged, the second line, as the axillary, are also commonly affected. This has been called the *ulceroglandular type* and accounts for the great majority of the cases.

If the eyes be rubbed by hands upon which there is infected material the conjunctiva becomes the site of the primary lesion and the regional glands are likewise affected. This is called the *oculoglandular type*, but in no way except for the position of the primary sore does it differ from the so called ulceroglandular variety. In fact it would seem an artificial distinction to differentiate them. A multiplicity of types of syphilis depending upon the site of the chancre could with equal reason or unreason be so differentiated. The conjunctiva is intensely congested and edematous with pronounced photophobia and lachrimation. Keratitis may also be present.

In 85 per cent of the cases the portal of entry can be identified and the regional glands are occasionally not enlarged. In the other 15 per cent the portal of entry cannot be located. In some there is a pronounced general adenopathy and these have been classified as the *glandular type*. The remaining cases have presented no conspicuous glandular enlargement and have been called the *typhoid type*, these usually occur among laboratory workers. The exact method of infection in these cases without a detectable primary lesion is still a matter of doubt. The following suggestions have been made—ingestion inhalation or via the skin without producing a local lesion. This is further substantiated by visceral lesions such as the following.

*Pleuropulmonary tularemia* produced by inhalation of the organism. The onset is fairly abrupt with nonproductive cough, dyspnea, fever, malaise and pleural pain is prominent. It differs but little from the secondary lesions mentioned below. It is usually only recognized by finding the specific bacterium isolated from mice inoculated with sputum.

*Gastrointestinal tularemia* results from ingestion of the bacterium usually through eating undercooked rabbit meat heavily infested. There may be produced a severe necrotizing lesion in mouth, pharynx and nasopharynx with enlargement of the neighboring glands. Nausea, vomiting and severe abdominal cramps with diarrhea may follow. Cases are reported with a fulminating course particularly in children.

The general features of tularemia are an irregular fever seldom above 104° F, usually about 102° resembling that of sepsis. Repeated chills are common. There is tachycardia in proportion. The spleen is enlarged and frequently palpable as is also the liver. There is a mild polymorphonuclear leucocytosis (35 thousand have been reported in occasional cases). The visceral lesions are principally in the serous cavities producing pleuritis, peri-

which may be confirmed by finding the anthrax bacilli in the scrapings of this and by the Ascoli reaction. This is a simple precipitin test: a small amount of the infected material is mixed with 5 to 10 cc of salt solution, and when this has been filtered and cooled, it is poured upon a precipitating serum. A white donutlike ring forms which is characteristic of the infection. It is an important supplement to the bacteriological examination.

**Prognosis**—The prognosis is always serious, especially when the portal of entry is on the face or neck, or through the respiratory system, when the course is extremely rapid, death occurring usually within forty-eight hours. On the other hand if the primary lesion is on the hand or arm, a longer period elapses before a general infection occurs and during this period much may be done.



Fig. 442.—Anthrax. Infection on shaving brush. (From Sutton and Sutton: Diseases of the Skin.)

**Treatment**—Prophylaxis is naturally most important. This may be approached by sterilization of skins and hides which may be infected, and the vaccination of cattle, sheep, and human beings who may be exposed to the infection through environment or contact. Curative treatment is difficult when the primary lesion is on the face or neck or through the gastrointestinal or respiratory system. The principal hope is when the primary lesion is on the hand or arm. No time should be lost in giving massive doses of anti-anthrax serum. Penicillin has produced an excellent response in the small number of cases so far reported. It should be given in full doses of 480,000 O.U. in 24 hours (see Chapter XX) combined with antianthrax serum. Local surgical procedures have been discarded as they frequently change a local into a general infection. Irrespective of what treatment is used, success depends upon an early diagnosis.

## GLANDERS

**Synonyms**—Farcy, equinia, malleus.

**Definition**—Glanders is an acute or chronic infectious disease due to the *Malleomyces mallei* and is contracted by man from horses, mules, and other equina through the skin and mucous membrane.

one of the first organisms to be identified with disease. It forms spores which are extremely resistant to heat and ordinary disinfectants. They persist in the soil for a long time and are distributed in pastures and other areas by the excreta of infected animals or from their dead bodies even when buried. All animals, including man, and birds are susceptible but it is more commonly found in cattle and sheep.

**Symptoms and Signs**—In cattle, sheep, and other herbivorous animals the infection gains entrance through their food being contaminated by spores of the bacilli. In man it may gain entrance through the inhalation of dust as in wool sorters when sheep's wool is infected. There have been reported cases infected through biting insects carrying the bacilli and inoculating them through skin abrasions. Water borne infection has occurred when the refuse and washings of infected hides, etc., have been washed down a water shed to infect wells or other sources of drinking supply. But the most important portal has been through casual skin cuts or abrasions by those handling hides or using cheap shaving brushes which harbor anthrax spores.

The incubation period is twelve hours to two days. The primary lesion is usually on the face or hands. It begins as a small red area like an insect bite which soon forms a vesicle with surrounding induration and edema. There soon develops a black gangrenous center with spreading edema and adjacent crops of vesicles which coalesce and eventually form a rather large, hard, indurated and necrotic area from which a slough separates hence the name malignant pustule. There is no suppuration. The neighboring lymph glands in a few days become enlarged. The general symptoms are moderate pyrexia, head ache, nausea and general muscular pains. The pulse is weak and rapid with great prostration and collapse. There are few localizing symptoms in this general systemic infection.

When the bacilli are ingested, there are the usual systemic symptoms and in addition the whole gastrointestinal tract from the nose and nasopharynx to the rectum is intensely congested and hemorrhages occur from the mucous membranes. Intense bloody diarrhea and hematemesis are common. Visceral lesions sometimes also occur and are called internal anthrax. In this form there are few or no distinctive features.

In spite of the malignant character of the disease the patient has little or no pain nor is conscious of the seriousness of his condition and death may occur within forty eight hours, especially if the portal of entry is via the face or eyelids. In the respiratory form of the disease when there is laryngeal, tracheal, bronchial and pulmonary infection there is intense congestion and rapid systemic dissemination with cerebral symptoms, collapse and death. Pneumonic signs may develop but these are rare due to the fulminating character of the infection.

The *pathological anatomy* is principally an intense necrosis or in the more areolar tissues edema is the dominant feature. The local lesion is practically the only one which is characteristic of the disease and if not recognized the true pathological process may be overlooked.

**Diagnosis**—The diagnosis rests entirely upon the recognition of the possibility of an anthrax infection through the character of the primary lesion.

sometimes difficult on account of their small numbers. Strauss has introduced an important diagnostic method. If some of the pus or hemorrhagic discharge from an ulcer be injected into the peritoneum of a guinea pig an acute purulent orchitis will develop after twenty four to thirty six hours from which the *M. mallei* may be readily isolated.

**Prognosis**—The course of glanders varies a great deal. In the acute variety death usually occurs within a short time from pneumonitis or general sepsis. In the chronic form it may last for many years particularly if the lesions remain superficial and the viscera are not involved.

**Treatment**—*Prophylaxis*—As the disease is contracted from an infected horse or other equines these should be destroyed as soon as detected and their stables harness blankets and drinking buckets and troughs disinfected.

The treatment of an active case is principally symptomatic. The local abscess should be treated surgically and with the thermocautery. The general regime is that of an acute or chronic infection comprising rest, good diet, fresh air, and fluids. Specific treatment has been unsatisfactory. Vaccine therapy has been advocated as has also injection of mallein but the benefits are indefinite. Many drugs have been used, such as mercury inunctions, creosote, potassium iodide, sodium benzoate internally, iodine, ichthyol, phenol with alcohol, hydrogen peroxide, boric acid and potassium permanganate locally. Their number indicates the dubious benefit of any.

## TETANUS

**Synonyms**—Lockjaw, trismus.

**Definition**—Tetanus is a specific infectious disease caused by the *Clostridium tetani* which produces toxins with a close affinity for the central nervous system leading to local and general tonic spasms.

**Etiology**—The *C. tetani* is shaped like a drumstick with a spore at one end. There are nonspored forms which have rounded ends and are actively motile. It is gram positive and absolutely anaerobic and is found in the soil. It has a natural habitat in the intestinal tract of herbivora who spread the infection by their droppings. The distribution and concentration of the organism in the soil vary considerably in different parts of the world.

It gains entrance to the body through wounds, particularly penetrating ones such as those due to a nail or other sharp object, gunshot or shrapnel wounds especially when infected cloth is carried in with them. Operations about the rectum or perineum are occasionally a portal of entry as are also dirty vaccination wounds. Rarely a case develops without any history of injury. These are supposed intestinal infections. There is a high incidence of the disease in July due to the entrance of the bacilli through burns from fire crackers but it is most common in the summer months and in warm climates as compared to the winter and arctic regions.

**Symptoms and Signs**—The incubation period is from one to three weeks and depends to some extent upon the situation of the portal of entry. If it be in the distal part of an extremity it is longer than when in the face or neck. There are no symptoms at this time and the wound may have been forgotten,

**Etiology**—It is due to *M mallei* which is usually a straight rod shaped organism, although occasionally it is slightly curved. It measures 3 to 4 microns in length, and 0.5 in width. It is nonspore bearing and nonmotile, and stains easily but irregularly, giving a beaded appearance, and is gram negative. It grows easily on artificial media, particularly potato, where it forms a slimy growth which gradually changes from a yellowish to dark red dish brown color.

**Symptoms and Signs**—The incubation period of glanders may range from three days to four weeks. The portal of entry is through the skin, and the disease is chiefly contracted by those occupied with horses, particularly farmers, hostlers, grooms and stableboys. The onset may be either acute or chronic.

**Acute glanders** begins with malaise, headache, nausea, vomiting and general pains. There may be chilliness, but seldom rigors, with an irregular pyrexia. In some cases the onset is more violent and the symptoms are those of a respiratory infection closely simulating pneumonia. Arthritic signs may be a prominent feature suggesting acute rheumatic fever. A fourth group for a time have no localizing signs and imitate typhoid fever, miliary tuberculosis or subacute bacterial endocarditis. After a few days skin abscesses appear with an intense local reaction, and from them there is a spreading lymphangitis along the course of which small hard nodules or "farcy buds" develop. Similar abscesses may appear on the mucous membranes of the nose, pharynx and larynx, and in the lungs and pleura. In all there is necrosis with suppuration. The lesions in the skin may be so numerous as to suggest smallpox.

**Chronic glanders** has an insidious onset without general symptoms. There appear, first on the skin usually of the hands, arms or face, one or more nodular swellings which suppurate, become necrotic and form an indolent ulcer from which there is a sticky discharge. The ulcers are usually multiple. They may heal, but it is the rule for others to develop locally or at a distant site. The infection may remain dormant for years and then reappear. The mucous membrane of the nose and nasopharynx is a favorite site for chronic glanders to persist, resembling a chronic nasal catarrh with mild local signs and no constitutional symptoms.

**Pathological Anatomy**—Although the *M mallei* usually gains entrance through the skin or mucous membrane, the diffuse lesions are hematogenous and abscesses may be found in the lungs, pleura, larynx, liver, spleen, muscles, bones, and joints. The lesion is between a tubercle and an abscess. The nodules are dense collections of epithelioid cells and leucocytes. They soon undergo necrotic disintegration and liquefaction with the formation of irregular ulcerations which heal slowly, forming raised scars as in syphilis.

**Diagnosis**—The diagnosis of glanders is often difficult. With the reduction in the use of the horse as a beast of burden it has become a comparatively rare disease. The character of the nodules and ulcers might suggest syphilis or tuberculosis, while the systemic symptoms require its differentiation from rheumatic fever, pneumonia, miliary tuberculosis, typhoid fever, etc. The finding of the *M mallei* in the pus makes the diagnosis complete, but this is

neurosis with hyperventilation which, producing an uncompensated gaseous alkalosis and severe tetany, is easily confused with tetanus. An absolute diagnosis may be made by finding the *Cl. tetani* in the tissues at the portal of entry even though it has seemingly healed.

**Course**—The course of the disease varies somewhat. There are patients in whom the symptoms remain localized in one area and may develop many weeks after the initial lesion. In these the infection has been small in amount or for some reason the bacilli have been in an indifferent tissue environment. Some of these recover. If general symptoms develop before specific treatment has been started the death rate is practically 100 per cent, while if specific treatment has been given and symptoms then occur they may be mild with recovery. This, however, is not always the case as some progress to a fatal issue. It is not unusual for symptoms to develop many weeks after the initial infection, in fact a piece of shrapnel imbedded in tissue may harbor the bacilli and when an attempt is made to remove it tetanus may ensue due to the aggravation of the local infection.

**Treatment**—*Prophylaxis*—Every suspicious wound which means those received in warfare from firecracker burns from penetrating wounds about barnyards or on the public streets should be thoroughly cleansed, extirpated and exposed to oxygen by either free access of air or pure oxygen, and specific antitoxic serum should be immediately administered. Protection before injury may be afforded to gardeners blacksmiths cattlemen and soldiers by the periodic prophylactic injection of 1500 units of antitoxic serum in four weekly doses. This however is of temporary benefit (18 months) and may lead to a false security. Active immunity by the injection of an anatoxin toxoid is relatively permanent.

If prophylactic protection has not been given 50 000 units of tetanic antitoxic serum should be injected intravenously and an equal amount intramuscularly as soon as the first sign or symptom appears. These amounts should be repeated daily until there is a definite reduction in spasms and then every other day until these cease. Others advocate 200 000 units (one half the total dose given intravenously and one half intramuscularly) the first day and repeating in amounts of 80 000 units daily. In the meantime the tonic and clonic spasms should be controlled by the intravenous injection of 50 cc of a 20 per cent solution of magnesium sulfate as often as is necessary to control them. It is not curative but palliative to reduce the colossal expenditure of energy caused by the spasms. Many other drugs have been advocated for the same purpose such as curarine and ethylenediamine. A moderate anesthetic state obtained with avertin or allied drugs is probably the best method of reducing the effect of external stimuli. In addition to all such therapy the patient should be kept absolutely isolated from all external stimuli in fact, should be kept metaphorically wrapped in cotton wool. The greatest difficulty is a food supply. A continuous intravenous injection of glucose and amino acids or a balanced liquid diet given by an indwelling gastric tube through the nose over days is sometimes the only rational method. Both require constant attention however. Hydrotherapy for the control of pyrexia may be used but at this stage the end is not far off.

when there is felt a stiffness in the opening and closing of the mouth and a sense of apprehension and restlessness with frequent yawning. There may then be some discomfort at the site of the wound.

After a few days the tonic spasms of the masseter muscles become so strong that the mouth cannot be opened and attempts to do so cause exquisite pain. The spasticity rapidly spreads to other muscles of the face and neck. The face has a perpetual grin or grimace and there may be opisthotonos. The patient becomes intensely sensitive to all external stimuli which now produce clonic spasms, and this is called the hyperesthetic stage. These clonic reactions may be local or general. They occur with increasing frequency and from the slightest stimulus, such as a noise, an increased light, a current of air, or the slightest touch to the bed or bedclothes. The diaphragm may be particularly involved and seriously interfere with respiration.

During the second week of symptoms the terminal stage usually develops. The pain is now intense, there are urinary retention, pronounced pyrexia, sometimes hyperpyrexia, sweating, exhaustion and death. The ghastly feature of the termination is the mental alertness of the patient to the end.

With the increasing intensity of the tonic and clonic spasms the muscular energy expended demands a greatly augmented supply of oxygen, so although true basal oxygen demands cannot be estimated the oxygen consumption may rise to tremendous amounts. There is a parallel heat production which cannot be dispersed and in consequence the body temperature rises. There is also a pronounced tachycardia not due to a direct intoxication but to the demands of an excessive and constantly increasing blood flow per minute. The systolic blood pressure rises as in physical exercise, but toward the end falls from exhaustion and cardiac failure. Otherwise physical examination is negative.

**Pathological Anatomy**—The pathological anatomy of tetanus is not specific. There may be some degenerative lesions of nerve cells and petechial hemorrhages in the brain and cord. There is no evidence that these are in any way specific. The *Cl. tetani* produces two toxins tetanolysin and tetanospasmin. The latter produces the picture described above. It is taken up by the motor end plates in the tissues of the portal of entry and ascends along the axis cylinder or lymphatics of the nerves to the motor ganglia of the cord and brain. The manner of its effect is not agreed upon. There are two contentions, (a) that the tetanospasmin renders the nerve cells more sensitive to stimuli and (b) that it removes the power of inhibition so that there is an unchecked response to slight stimuli which normally would be compensated for.

**Diagnosis**—This disease may be confused with strychnine poisoning, rabies, tetany, meningitis and hysteria but the history and suitable examinations should readily clarify the picture. The first can only be suspected by the immediate history of accidental or suicidal administration of the drug. Rabies follows a dog bite. It is true that many weeks or months may have intervened. A lumbar puncture proves or disproves meningitis. Tetany and hysteria give greater difficulty particularly in the first attack of a respiratory



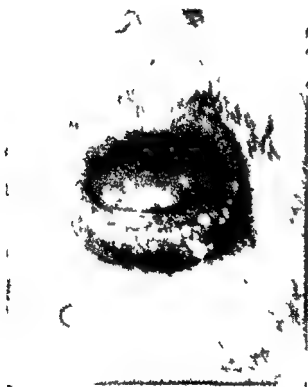


Fig. 48a—Photomicrograph showing the effect of introduction of the cells of the calyx of *Dr. Paul W. C. L. H. F. m. Saff. n. n. Saff. n. D. y. s. t. the Saff. n.*

## FOOT AND MOUTH DISEASE

**Synonyms**—Epidemic stomatitis, aphthous fever

**Definition**—Foot and mouth disease is a specific infectious disease of cloven foot animals (especially cattle, sheep, and pigs) and man. It is caused by a known filterable virus and is characterized by vesicles appearing on the mucous membrane of the mouth, pharynx, lips, and the skin between the fingers and toes. It is contagious.

**Symptoms and Signs**—The incubation period is between four and ten days, and the portal of entry is through the skin of the hands or the mucous membrane of the mouth and lips. The onset is fairly sudden with general malaise, headache, vomiting and pyrexia. There is diarrhea at first and then constipation. After a few days (three to eight) there is felt a burning sensation of the hands, feet and mouth. The former show a transitory exanthem while the mouth and lips are intensely red. Soon small vesicles appear on the mucous membranes and sometimes between the fingers and toes (Figs 483 and 484). The vesicle is yellow with a red areola and at first contains clear fluid which becomes turbid, and it finally breaks leaving a shallow ulcer. Those on the skin become dry and scaly. They all heal without scarring. The mouth is sore and mastication is painful. The tongue is heavily coated with a slimy film and there is profuse salivation and the breath is fetid. The disease terminates in about three weeks in recovery.

**Diagnosis**—This disease is to be differentiated from herpes, pemphigus and other forms of aphthous stomatitis. The distribution of the eruption excludes the first, the presence of fever the second and the constitutional reaction and lesions on the fingers and toes the third. The diagnosis is confirmed by guinea pig inoculation and the demonstration of the presence of the virus by cross immunity reactions.

**Treatment**—Strict isolation is imperative and those working with infected animals should take every precaution to avoid contamination. Milk from such cattle should be discarded or boiled before using and never fed to pigs. The individual case is treated by general symptomatic measures. The mouth should be frequently irrigated with a bland antiseptic solution in large quantities and to painful ulcers silver nitrate should be applied.

## INFECTIONS DUE TO THE BITES OF MAMMALS

Human beings are not infrequently bitten by other human beings, dogs, cats, horses, camels, rats, etc. The majority of these injuries produce no other lesion than that due to pyogenic or necrotic organisms. Probably the worst of such are those due to the human bite when a foul infection due to the organisms of dental caries and pyorrhea produces an indolent, sloughing wound. In addition to these there are two specific infections transmitted by mammalian bites which in themselves are locally comparatively clean but the general dissemination of the virus produces most profound and specific results. They are rabies and rat bite fever.



Fig. 48c.—Foot and ankle in disease. The large illustration of the ankle is typical (Courtesy of Dr. Paul W. Clark). From Sutton and Little, *Diseases of the Skin*.





Fig. 484.—Foot and mouth disease in man showing character and distribution of lesions on the hands. (Courtesy of Dr. Paul W. Clough. From Sutton and Sutton, Diseases of the Skin.)



## Rabies

**Synonyms** —*Hydrophobia* *lyssa*

**Definition** —Rabies is a specific infection of canines and man. It causes great excitability and mental derangement. It is caused by a filtrable virus which is destroyed by drying heat and chemicals.

**Etiology** —The virus may be passed from man to man through bites but man is most usually infected by the bite of a rabid dog and less often by a fox or wolf. One of the earliest cases recorded in Canada is the death of General Simcoe, Governor of Upper Canada, from the bite of a wounded but rabid fox. The virus is present in the saliva of a rabid animal. The distribution of the disease throughout the world is quite irregular. It is common in India, France, Spain, Italy, and other Mediterranean countries. In Great Britain it is rare and in Australia it does not exist because of the strict canine quarantine in both countries. In North America there are spotted foci of infection through many states. In Canada there has always been an endemic area in central Ontario but until 1926 there had never been a recorded case east of Kingston, Ontario. In that year, through lack of proper canine quarantine regulations, it spread eastward through Ontario and Quebec but now appears to be again extinct.

**Symptoms and Signs** —The virus is always introduced through the bite of a rabid animal which may have healed and been forgotten long before the initial symptoms appear. Therefore the portal of entry may be indefinite. The incubation period may vary from six weeks to six months or even a year. This prolonged lapse of time is characteristic of the disease and during this period there are no symptoms. The first indication is a soreness or numbness at the point where the bite was inflicted. This is soon followed by dysphagia, dyspnea, and dysarthria. These are due to a hypersensitiveness of normal reflexes. This is soon followed by definite spasms, particularly of the muscles of the pharynx, larynx, and diaphragm. The slightest stimulus of sight, sound, smell, or the desire to swallow may initiate a painful spasm. It is from this last symptom, initiated by the sight of water, that the dehydrated individual suffers the most acute agony, hence the synonym 'hydrophobia' or fear of water. The spasms are intermittent and may cause a castanet-like sound through the clicking of the teeth. The voice is husky and the laryngeal spasms may eject a cry likened to a dog bark. This stage is accompanied by fear, mental excitation, delusions, hallucinations, and even mania. It lasts several days and is followed by a state of depression and exhaustion which soon progresses to coma and death.

During the stage of excitation there is pyrexia due somewhat to toxemia but principally to the excessive muscular activity. There is increased oxygen consumption, sweating, tachycardia, thirst, and finally vasomotor collapse with pallor. Respiration may be sufficiently embarrassed to produce dyspnea and cyanosis. All these symptoms are due to functional disturbances resulting from the spasms and closely resemble tetanus (see page 1341).

**Pathological Anatomy** —The pathological anatomy reveals in the ganglion cells of the cerebral and cerebellar cortex the typical and diagnostic

*Negri bodies* which are pathognomonic of the disease. They are reddish masses with black dots within the cells. There is a dispute as to whether these are the infecting organism or whether they are the result of cellular disintegration. In addition the ganglion cells are degenerated and there are leucocyte infiltrations, and petechial hemorrhages in the brain and also throughout the viscera which are greatly engorged.

**Diagnosis**—This is not difficult although it may at first be unsuspected if the history of a dog bite is not forthcoming. It must be differentiated from tetanus, focal epilepsy, and hysteria. Every vicious dog which bites a person should be put in quarantine until it is found rabid or not. Its saliva may be injected into the brain of a rabbit which will promptly die of rabies. If there is any doubt it should be killed and its brain examined for *Negri bodies*. This is the only method of arriving at a definite diagnosis before it is too late to institute specific treatment.

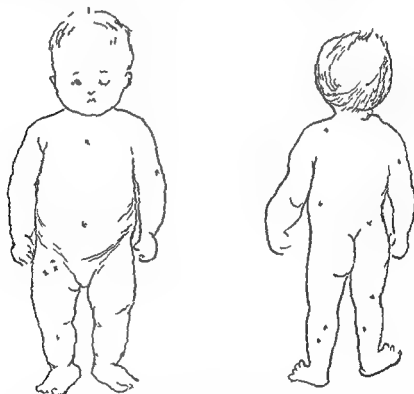


Fig. 485.—Distribution of rash in same case as Fig. 486

**Prognosis**—Once the symptoms develop, death always occurs within a few days. The earlier the specific vaccination is started the better the results.

**Treatment**—The successful treatment of rabies depends entirely upon the recognition of the possibility of infection during the incubation period when the patient may be immunized so that when it is over, there is complete protection, which emphasizes the importance of ascertaining whether or not the dog or other animal that bites a person is rabid. If this is not done, the possible diagnosis is purely speculative and unfortunately people are prone



to give the benefit of the doubt in favor of the animal's not being rabid or kill the animal without being certain.

The vaccine is prepared by a number of methods. They all depend upon some manner or other of attenuating the virus. It is obtained from the brain and cord of an infected rabbit which is dried at a constant temperature over potassium hydroxide and then emulsified in salt solution. In the original Pasteur vaccine it was preserved in 50 per cent of glycerine with about 0.5 per cent of trichresol. In addition the following methods have been employed:

*Cummings*—dialyzed against tap water

*Hayes*—different dilutions of a glycerine emulsion

*Semple*—1 per cent phenol emulsion

*Harris*—tissue dried in CO<sub>2</sub> snow

Vaccines prepared by certain of these methods may be obtained from pharmaceutical firms or from public health departments with complete instructions as to their use which should be meticulously followed. The course of treatment usually extends over 14 to 19 daily injections, each inoculation being properly numbered. These preparations have done away with the necessity of the Pasteur Institute treatments of years ago. There is no difficulty for any physician carrying out this treatment.

Occasionally (1 in 5000) cases so treated develop a peripheral paralysis. There is no proved explanation for such and they are principally of academic interest.

### Rat-Bite Fever

**Synonyms**—*Sodoku* or *sokoshu*. Haverhill fever.

**Definition**—This is a specific infection following the bite of an infected rat. It has been reported as resulting from the bite of other rodents and also of a cat. Although it is common in Japan, isolated cases are reported from other countries both in Europe and America.

**Etiology**—This disease may be caused by one of two organisms or both. These are the *Spirillum minus* and the *Streptobacillus moniliformis*. Although this disease is primarily a disease of wild rats, it may be transmitted to man by other animals which have been bitten by infected rats, such as the dog, cat, mouse, and white laboratory rats. As will be seen later, it is important to differentiate which organism is responsible or whether both are. This can to some degree be determined by the clinical course, but best by the isolation from the patient of the specific agent.

**Symptoms and Signs**—After the rat bite there is an indefinite incubation period ranging from 5 to 21 days in the *spirillum* type. The bite wound is usually healed. The onset is sudden with pyrexia and often a chill. There are headache, malaise, general muscular pains, sweating, and the other signs of a general infection. The site of the bite becomes painful, tender, swollen, and reddened (see Fig. 486). There is surrounding edema and a spreading lymphangitis. The tissues are often incised for non-existent pus. After a few days the pyrexia disappears and patient feels well. There is a remission of four to six days and another paroxysm occurs which lasts about forty-eight hours. With each paroxysm an erythematous bluish red rash appears. It

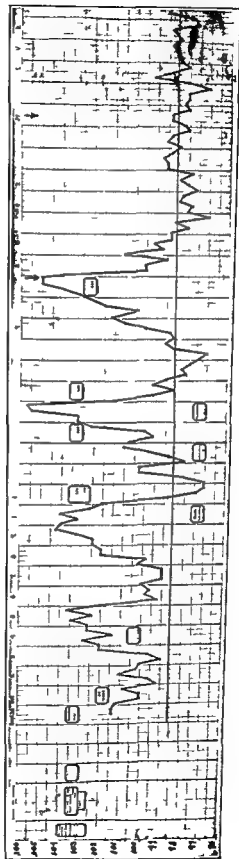


Chart XXV —Temperature chart in a case of rat bite fever



Fig. 386.—An illustration representing the acute excitation of the original local lesion in rat fever.



is discrete papular and clear cut varying in size and is distributed over the trunk and limbs (see Fig 465). With each return of pyrexia the rash and the local disturbance about the bite wax and wane. The neighboring glands are enlarged. There is a leucocytosis with an eosinophilia and lymphopenia. Severe anemia may eventually develop.

In the streptobacillary form the incubation period is one to three days. The bite heals promptly unless infected and does not show induration, inflammation or adenitis during the continuing course of the disease. The relapses of pyrexia are not so regular.

In both forms joint pains, arthritis, delirium and coma may appear. It is interesting that a false positive Wassermann may occur in both forms but more commonly in the spirillar form as do also the severe toxic symptoms.

**Pathological Anatomy**—The pathological anatomy shows but few changes. The local lesion is a granuloma which does not suppurate unless secondarily infected while there are local necrosis and round celled infiltration. This latter also occurs about the blood vessels in the rash.

**Diagnosis**—The diagnosis is not at all difficult if the original bite is noted and the significance of the local recrudescence and rash are appreciated. The recurring paroxysms suggest relapsing fever or malaria. But there should be little confusion. In absolute diagnosis can be made by finding the parasite in the blood stream but this is more difficult than would be expected. This is best done in spirillar form by inoculating white mice or guinea pigs with the patient's blood, exudate or tissue from the original lesion or lymph juice is piped from the regional nodes. The streptobacillus may be isolated by blood culture or lymph juice on special media. Agglutinins to this bacillus may be found in the patient's serum as early as the tenth day.

**Course**—The course in untreated cases may last for weeks or months. Fulminating cases occur but are rare as are those without pyrexia. Abortive cases which are unrecognized no doubt also occur. Death results occasionally from exhaustion, anemia, emaciation and secondary infections. The mortality was once stated to be about 10 per cent but this is much too high being more like 1 per cent.

**Treatment**—This is specific. The local lesion at the site of the bite should not be incised and arsenic in the form of arsphenamine or neoarsphenamine should be given in the usual doses (0.1 to 0.6 gm.) in the spirillar type. Usually two or three injections are sufficient but sometimes ten or more are required.

Penicillin has been found to be most efficacious in both types. In fact it will probably replace arsenicals entirely (see Chapter XX).

## DISEASES CARRIED BY LICE, FLEAS, TICKS AND OTHER BITING INSECTS

Lice, fleas and ticks play an important role in the transmission of disease from animals to man. These insects principally infect the rodent population of a community and spread the infection among these animals. If such an infection reaches epidemic proportions increasing numbers of these in

sects harbor the infecting agent and therefore augment the possibility of its transmission to man, as they can transmit it not only from the lower animals to man but also from man to man. It is after this manner that these epidemics begin and spread. An example of such a transmission has already been mentioned in tularemia where in some areas instead of man being infected directly from the rabbit, the tick may act as a vector. The virus is not inoculated into man by these insects but usually gain entrance by the excreta or crushed bodies of the insects being rubbed into abrasions or scratches.

Most of the diseases carried by biting insects are caused by Rickettsia. These are analogous to bacteria distributed amongst ticks, mites, spiders, and insects. There have now been identified three groups of human rickettsial diseases, namely (1) the typhus—louse and flea vector group, (2) the Rocky Mountain spotted fever—tick vector group, and (3) the tsutsugamushi—mite vector group.

The first group comprise epidemic European type of typhus fever and the murine type which is endemic throughout the world and has its natural reservoir in the rat.

The second group include Rocky Mountain spotted fever, São Paulo typhus of Brazil (and other South American states), the fièvre boutonneuse of the Mediterranean littoral, South African tick bite fever, and Kenya fever.

The third group consist of tsutsugamushi disease of Japan (scrub typhus), rural typhus of Malaya, and the mite fever of Sumatra.

The principal Rickettsial diseases, their general geographical distribution, and vectors are found in Table XX.

TABLE XX

DISEASE	GEOGRAPHICAL DISTRIBUTION	VECTOR
Typhus exanthematicus	Europe, Asia Minor, Persia, North China, Abyssinia, North Africa, Congo, Mexico	Louse ( <i>Pediculus humanus</i> )
Epidemic or typhus	World wide	Rat flea
Trench fever†	Western Europe, North Africa	Louse ( <i>Pediculus humanus</i> )
Rocky Mountain spotted fever (eastern and western types)	United States and Western Canada	<i>Dermacentor andersoni</i> <i>D. variabilis</i>
South African tick typhus	South Africa, Kenya, Abyssinia	Ticks
São Paulo rural typhus	Southern Brazil and South America	Ticks
Q fever	Australia and United States	Ticks
Tsutsugamushi disease (scrub typhus)	Far East, India, Malaya, Burma, New Guinea, Formosa, Japan, etc.	Larval mite of <i>Trombicula akamushi</i> <i>T. deliensis</i> <i>T. fletcheri</i> <i>T. walchi</i>
Carrion's disease	Narrow valleys of the Andes at altitudes of 2000 to 9000 feet in Peru, Ecuador, Chile, Bolivia, and Colombia	Small fly ( <i>Phlebotomus noguchii</i> and <i>P. verrucarum</i> )

## Typhus Fever

**Synonyms**—Brill's disease jail fever camp fever, ship fever, Fleck typhus Fleckfieber tabardillo typhus exanthematicus, spotted fever

**Definition**—Typhus fever is a specific infectious disease characterized by an abrupt onset, a purpuric eruption great prostration and a crisis about the tenth to fourteenth day. It is conveyed by lice and fleas. There is every reason to believe that for generations many diseases passed in the disguise of this infection as the many popular names indicate and its rough similarity to relapsing fever, typhoid fever trench fever epidemic meningitis and Rocky Mountain spotted fever to which the synonym of "spotted fever" should alone be applied.



FIG. 11.—Photograph showing the rash in typhus. (Courtesy of Dr. J. L. Todd.)

**Etiology**—In 1909 Nicolle demonstrated that the cause of European typhus fever was transmitted from person to person by lice. Since then great advances have been made in the control of this disease especially through the knowledge of the fact that the American variety is also conveyed by the rat flea which not only conveys it from rat to rat but also from the rat to man. The disease is caused by the *Rickettsia prowazekii*—almost simultaneously described by Ricketts and Prowazek. These Rickettsia are minute (1 to 1.5 microns long) gram-negative rod-shaped bodies. They often appear in coccoid form particularly in the feces of the louse or flea. They are deposited on the skin by these parasites and are rubbed into the skin through the punctures made by them or abrasions caused by scratching. The evidence favoring *Rickettsia* as the cause of typhus fever is overwhelming. The constant association of the *Rickettsia prowazekii* whether in lice guinea pigs other laboratory animals and men as well as the specific immunological studies and tissue cultures all weave a web of proof that is practically incontro-

sects harbor the infecting agent and therefore augment the possibility of its transmission to man, as they can transmit it not only from the lower animal to man, but also from man to man. It is after this manner that these epidemics begin and spread. An example of such a transmission has already been mentioned in tularemia where in some areas instead of man being infected directly from the rabbit, the tick may act as a vector. The virus is not inoculated into man by these insects but usually gain entrance by the excreta or crushed bodies of the insects being rubbed into abrasions or scratches.

Most of the diseases carried by biting insects are caused by Rickettsia. These are analogous to bacteria distributed amongst ticks, mites, spiders, and insects. There have now been identified three groups of human rickettsial diseases, namely: (1) the typhus—louse and flea vector group, (2) the Rocky Mountain spotted fever—tick vector group, and (3) the tsutsugamushi—mite vector group.

The first group comprise epidemic European type of typhus fever and the murine type which is endemic throughout the world and has its natural reservoir in the rat.

The second group include Rocky Mountain spotted fever, *Sao Paulo typhus of Brazil* (and other South American states), the *fièvre boutonneuse* of the Mediterranean littoral, *South African tick bite fever* and *Kenya fever*.

The third group consist of *tsutsugamushi disease of Japan* (*scrub typhus*), *rural typhus of Malaya*, and the *mite fever of Sumatra*.

The principal Rickettsial diseases, their general geographical distribution, and vectors are found in Table XX.

TABLE XX

DISEASE	GEOGRAPHICAL DISTRIBUTION	VECTOR
Typhus exanthematicus	Europe, Asia Minor, Persia, North China, Abyssinia, North Africa, Congo, Mexico	Louse ( <i>Pediculus humanus</i> )
Endemic or typhus	World wide	Rat flea
Trench fever?	Western Europe, North Africa	Louse ( <i>Pediculus humanus</i> )
Rocky Mountain spotted fever (eastern and western types)	United States and Western Canada	<i>Dermacentor andersoni</i> <i>D. variabilis</i>
South African tick typhus	South Africa, Kenya, Abyssinia	Ticks
São Paulo rural typhus	Southern Brazil and South America	Ticks
Q fever	Australia and United States	Ticks
Tsutsugamushi disease (scrub typhus)	Far East, India, Malaya, Burma, New Guinea, Formosa, Japan, etc.	Larval mite of <i>Trombidium akamushi</i>  <i>T. deliensis</i> <i>T. fletcheri</i> <i>T. tritarsus</i>
Carrión's disease	Narrow valleys of the Andes at altitudes of 2,000 to 9,000 feet in Peru, Ecuador, Chili, Bolivia, and Colombia	Sand fly ( <i>Phlebotomus neguchii</i> and <i>P. verrucarum</i> )



severity of the disease is influenced by the previous state and nutrition of the patient, the older the patient, the more serious the course and the higher the mortality. In childhood the disease is mild and death rarely occurs in those under twenty. Sex has no influence.

The principal complications in bronchitis and bronchopneumonia which in some epidemics account for much of the mortality. Other secondary infections in the salivary glands and middle ear sometimes occur. But in addition to the pulmonary lesions the most serious complications are due to arterial thromboses both visceral and cutaneous. This may occur in the mesenteric renal splenic cerebral pulmonary or any artery with organismal necrosis. Thromboses of the arteries in the skin and subcutaneous tissue account for the large area of superficial necrosis and gangrene (see Fig 488). Bad sores and symmetrical gangrene also occur. The relation to thromboembolism obliterans has been referred to (see page 466).

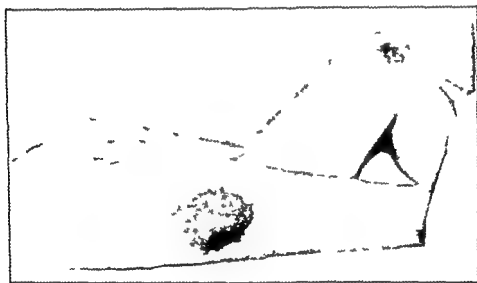


Fig 488—Photograph showing the rash in typhus with areas of purpura and gangrene. (Courtesy of Dr J. L. Todd.)

The mortality varies considerably in different epidemics from as low as 5 per cent to 70 per cent. In the mild endemic form in America it is probably about 3 per cent while in the severe outbreaks in Eastern Europe and Russia it was devastating.

**Diagnosis**—The early diagnosis before the appearance of the rash is difficult as the symptoms are like those of any acute infection which begins suddenly: Malaria relapsing fever pneumonia epidemic meningitis smallpox scarlet fever measles rat bite fever Rocky Mountain spotted fever etc. may have to be differentiated but this is not difficult as a rule once the rash has appeared except in those with a purpuric eruption.

The Weil-Felix agglutination reaction is constant after the appearance of the rash. This is performed with a standard culture of *B. proteus* which has been distributed to most bacteriological laboratories in the world. The test is done with either living or dead emulsions by the microscopic or macroscopic

vertible: There are also strong indications that the virus may remain dormant for many years, and this may explain the sporadic case in which neither lice nor fleas can account for the transmission of the disease when there is no source of the infection in the rest of the population.

**Symptoms and Signs**—The incubation period is from eight to twelve days, although in mild infections it may be longer. Toward the end of this time, the patient may have vague malaise and headache and even a slight pyrexia. But the real onset of the disease is sudden, with a chill, rigor, and high fever. There are considerable prostration and general pains. The alertness and mental excitation with flushed face and injected conjunctivae are striking features. Early delirium is common. The spleen is palpable, and anorexia and vomiting sometimes are present.

Between the third and the seventh day, usually on the fifth, a macular irregular erythematous eruption appears over the neck, thorax, abdomen, and extremities. There may also be a diffuse erythema which makes the maculae less obvious as these are not as a rule palpable, although sometimes they may assume large size and be felt. As the erythema fades, they become more apparent. The degree of the eruption is roughly proportionate to the severity of the disease. From a pink it gradually changes to a deeper pink then purplish and finally brownish color due to perivascular extravasations. In severe cases the rash is purpuric and there are then hematuria, hematemesis and melena.

The other manifestations are bronchial rales, cough and sputum due to a bronchitis which may extend to the bronchioles and cause a bronchopneumonia which is insidious in onset and is no way different from this lesion occurring in other diseases. There may also be present streptococcal or pneumococcal infections which may accordingly modify the pulmonary lesions. The pulse is always rapid, the blood pressure low, and signs of cardiovascular collapse are common in the severe cases. There is a moderate leucocytosis as a rule, with occasional high count which is an unfavorable sign. Intense delirium and nervous symptoms may closely simulate meningitis. They are more prevalent in typhus fever than any other acute infectious disease. The *endemic* or *murine typhus* is similar to the epidemic form except that it has a less severe symptomatology. The rash is less intense and extensive. Petechiae and purpura are less common and necrosis does not occur.

**Pathological Anatomy**—The pathological anatomy of typhus fever is microscopic rather than macroscopic. The spleen is large and soft but the chief characteristics are the "typhus nodules" of Fraenkel, which are perivascular infiltrations about the small vessels of the skin leading to thromboses and sometimes necrosis. Similar proliferative lesions occur about the small arteries, veins, and precapillaries including the central nervous system where they are particularly abundant and undoubtedly account for the intensity of the mental symptoms. Thromboses in the larger arteries and veins are not uncommon and account for the most serious of the complications.

**Course**—The course of this disease is usually from ten to fifteen days, when in favorable cases the temperature falls by crisis or rapid lysis. The

by an ulcer with a yellowish base. This primary lesion may be situated almost any place on the body except for the palms, soles and scalp. It should be carefully looked for. About the end of the first week a nonhemorrhagic macular or maculopapular rash appears on the trunk and may spread to the limbs.

The leucocyte count slowly rises to about 15 000 cells per cu mm but may be higher if complications develop. The Weil Felix reaction usually becomes positive during the second week but its absence should not exclude this disease.

The complications are most apt to develop during the second week and comprise pneumonia, encephalitis and circulatory collapse which vary greatly in intensity.

**Diagnosis**—The diagnosis depends largely upon the finding of the eschar and the general clinical pattern. Although the Weil Felix reaction occurs late it should be repeatedly tested for to confirm the final diagnosis. This disease should be differentiated from common diseases in the area such as malaria, infectious hepatitis and dengue.

**Prognosis**—The mortality in different localities would seem to suggest a variable virulence of different strains of *R. orientalis*. Other factors may be operative such as general nutrition and the presence of chronic diseases such as dysentery, malaria and so on. It varies from 1 to 60 per cent. The presence and severity of pneumonia is often the determining factor. Therefore although death may occur in the second week it is usually delayed until the third.

**Treatment**—Prevention depends upon avoidance of the vector. If this cannot be assured then the clothing should be systematically impregnated with a mite repellent such as dimethyl or methyl phthalate or benzyl benzoate.

As there is no specific cure for this disease the patient should be treated on those general lines appropriate to any acute infection such as bed rest, adequate caloric water and salt intake (the environment temperature and humidity being taken into account) and hydrotherapy. Oxygen should be given continuously in pneumonia with cyanosis.

Penicillin and the sulfonamides should be avoided unless there is a secondary infection (pneumonia) due to an organism which is sensitive to them. Recent reports suggest that para aminobenzoic acid may be effective as a chemotherapeutic agent.

### Trench Fever

**Synonyms**—Shin fever, shank fever, Meuse fever, Russian intermittent fever, Volhynian fever, five day fever, Polish fever, gaiterpain fever, His, Werner disease.

**Definition**—Trench fever is a prolonged recurring infectious disease with severe pains in the shins, prostration, splenomegaly and a rosy macular rash.

**Etiology**—This disease is probably caused by a Rickettsia (*R. volhynica*, *R. pediculi*, *R. quintana*) which is transmitted from man to man by the body louse. Therefore it often occurs in epidemics in overcrowded and unclean districts. It has not been described in civilian life but enormous numbers

**agglutination technic** A positive reaction, agglutination of 150 or higher, appears about the fourth day and reaches its maximum just before the crisis. It is specific except that it also is positive in Rocky Mountain spotted fever and tsutsugamushi disease (see below). The only certain method of differentiating these two is based upon the fact that guinea pigs which have recovered from typhus fever are immune but not to spotted fever, and vice versa.

**Treatment**—*Prophylaxis* is principally the extermination of lice and fleas, in other words delousing the whole population. All personal clothing, bed clothes and mattresses should be sterilized. Delousing of all bedding and clothes has been rendered much simpler by the generous use of DDT (dichloro diphenyl trichloro ethane). Attendants should be protected from contamination by these insects by wearing louse proof clothing, and in addition the head must be covered and rubber gloves worn. In epidemics especially all attendants should be careful not to transport these parasites on their clothes. Most successful results have been obtained by protective vaccination and there is hope that a curative serum may soon be available.

The *active treatment* is symptomatic as there is no specific remedy. A sufficient caloric diet should be assured and dehydration must be prevented by copious fluid intake. Pyrexia is controlled by external hydrotherapy and an ice bag constantly applied to the head is often beneficial for headache and delirium. In fact it is the same as for all acute febrile diseases. Particular attention should be directed to the prevention of bed sores and superficial gangrene which so easily develop. This is best done by careful protection to pressure points by air cushions and rings.

### Tsutsugamushi Disease

**Synonyms**—Scrub typhus, tropical typhus, rural typhus, Japanese river fever, mite borne typhus, kedani disease.

**Definition**—Tsutsugamushi disease is an acute specific rickettsial disease conveyed to man by a mite. The disease is chiefly characterized by a primary lesion at the site of the attachment of the mite and a macular rash.

**Etiology**—This disease is caused by *R. orientalis* (sometimes called *R. tsutsugamushi* and *R. nipponica*) which is transmitted to man by the larval form of several mites of the genus *Trombicula*. Of the many species of these mites, it would seem that only four are responsible namely *T. akamushi*, *T. deliensis*, *T. fletcheri*, and *T. ualchi*. The animal reservoir are certain field rodents.

**Symptoms and Signs**—The incubation period is ten to eighteen days and the onset is sudden with headache, chilliness and fever which rises gradually reaching a maximum of 102° to 103° F. during the second week, continues into the third week and then falls by lysis. The signs of general intoxication are increasing headache, anorexia, lethargy and sometimes a low delirium. The more local signs are conjunctivitis, deafness, regional lymphadenitis and bradycardia.

The area where the tick has been implanted is often the site of an eschar which represents the primary lesion. This may be a roundish ulcer averaging 5 to 7 mm. in diameter covered with a dark crust and surrounded by a pinkish elevated zone. In some areas the crust may not be present but is replaced

by an ulcer with a yellowish base. This primary lesion may be situated almost any place on the body except for the palms soles and scap. It should be carefully looked for. About the end of the first week a nonhemorrhagic macular or maculopapular rash appears on the trunk and may spread to the limbs.

The leucocyte count slowly rises to about 15 000 cells per cmm. but may be higher if complications develop. The Weil Felix reaction usually becomes positive during the second week but its absence should not exclude this disease.

The complications are most apt to develop during the second week and comprise pneumonia, encephalitis, and circulatory collapse which vary greatly in intensity.

**Diagnosis**—The diagnosis depends largely upon the finding of the eschar and the general clinical pattern. Although the Weil Felix reaction occurs late it should be repeatedly tested for to confirm the final diagnosis. This disease should be differentiated from common diseases in the area such as malaria, infectious hepatitis and dengue.

**Prognosis**—The mortality in different localities would seem to suggest a variable virulence of different strains of *R. orientalis*. Other factors may be operative such as general nutrition and the presence of chronic diseases such as dysentery, malaria and age. It varies from 1 to 60 per cent. The presence and severity of pneumonia is often the determining factor. Therefore although death may occur in the second week it is usually delayed until the third.

**Treatment**—Prevention depends upon avoidance of the vector. If this cannot be assured then the clothing should be systematically impregnated with a mite repellent such as dimethyl or methyl phthalate or benzyl benzoate.

As there is no specific cure for this disease the patient should be treated on those general lines appropriate to any acute infection such as bed rest, adequate caloric water and salt intake (the environment temperature and humidity being taken into account) and hydrotherapy. Oxygen should be given continuously in pneumonia with cyanosis.

Penicillin and the sulfonamides should be avoided unless there is a secondary infection (pneumonia) due to an organism which is sensitive to them. Recent reports suggest that para aminobenzoic acid may be effective as a chemotherapeutic agent.

### Trench Fever

**Synonyms**—Shin fever, shank fever, Meuse fever, Russian intermittent fever, Volhynian fever, five day fever, Polish fever, gaiterpain fever, His-Werner disease.

**Definition**—Trench fever is a prolonged recurring infectious disease with severe pains in the shins, prostration, splenomegaly and a rosy macular rash.

**Etiology**—This disease is probably caused by a louse (*R. volhynica*, *R. pediculi*, *R. quintana*) which is transmitted from man to man by the body louse. Therefore it often occurs in epidemics in overcrowded and unclean districts. It has not been described in civilian life but enormous numbers

of soldiers were infected during World War I and a lesser number during World War II, hence the name "trench fever" and most of its synonyms. The Rickettsia has been found in the blood, urine and tissues of those infected. It is supposed to gain entrance through the skin by the excreta or dead bodies of the louse being rubbed into the skin through scratches or other abrasions.

**Symptoms and Signs**—The incubation period is uncertain but is probably somewhere between fourteen to twenty eight days. The onset is sudden with a chill and pyrexia up to  $102^{\circ}\text{F}$  or  $103^{\circ}\text{F}$ , and tachycardia. This may be preceded by a short period of general malaise, headache, and muscular pains. But with the real onset, prostration, muscle and bone pains chiefly in the legs, and anorexia, become prominent symptoms. In addition there is splenomegaly and a fairly characteristic rash upon the chest and abdomen. It closely resembles the rose spots of typhoid fever. It consists of discrete red papules measuring a few millimeters to a centimeter in diameter. They disappear on pressure.

These symptoms and signs are not exclusively characteristic of trench fever but may simulate and be simulated by other infectious diseases except that the pains in the legs are conspicuously severe. The pyrexia is, however, of special importance in that it runs through recurring remissions and exacerbations, and with each there is a waning and a waxing of all the signs and symptoms including the rash. This periodicity is irregular, and recrudescences or relapses may recur after months or even years. It has also been demonstrated that the virus may remain viable for many months and lice may be infected from patients over a year after the onset of the disease.

There are, in addition to these symptoms and signs a mild bronchitis, and in the early stages moderate leucocytosis (12 000 per cu mm) but this fluctuates considerably and a leucopenia is often found. Anorexia with vomiting has also been reported.

**Pathological Anatomy**—This is not known as the disease is not fatal and therefore there has been no opportunity to make a complete examination. The only tissue which has been examined is the skin. Biopsy reveals the rash to be due to a lymphocytic perivascular infiltration with a few polymorphonuclear cells. Local necrosis does not occur.

**Diagnosis**—This as a rule, is comparatively easy when it occurs among troops or in other crowded and unsanitary areas. Sporadic cases are usually overlooked unless the patient suggests it himself from past experience. It is usually confused with influenza, typhoid fever, paratyphoid fever, rheumatic fever, relapsing fever, malaria, dengue and typhus fever. There is no specific test either by immunological or bacteriological diagnostic methods. The diagnosis must therefore rest upon clinical evidence.

**Prognosis**—The course of the disease is prolonged and relapses after prolonged periods are not uncommon but death does not occur. The disease however, leaves a chronic debility which may last for years and it would seem that the virus remains viable in man for a long time and may be the cause of these chronic and persistent disabilities.

**Treatment**—The treatment of trench fever is entirely symptomatic and such as is employed in all acute infections. Antipyretics, analgesics and

hydrotherapy are indicated in the management of the pains and pyrexia. The convalescence is prolonged and the patient must be guarded against too hasty return to active life. This is particularly so in soldiers who should be slowly and gradually reconditioned for strenuous training because physical signs are not detectable to contraindicate it although the symptoms of dyspnea tachycardia and precordial pain on exertion sweating and easy fatigue are significant of a continuing "debility." D. A. H. irritable heart or neurocirculatory asthenia all synonyms of the same syndrome (page 373).

The other Rickettsian diseases shown in Table XX present a clinical pattern similar to that of typhus although in general much less severe. In scrub typhus the bite of the larval mite may result in an ulcer with lymphangitis and adenitis. The rash usually commences on the face and does not become petechial. The death rate in these allied conditions is low and there is no known specific therapy. Symptomatic treatment for infectious diseases is indicated.

### Rocky Mountain Spotted Fever

**Synonyms**—Tick fever black fever

**Definition**—Rocky Mountain spotted fever is an acute specific disease caused by a Rickettsia called *Dermacentrozetes* and is conveyed to man by the wood tick. The disease is chiefly characterized by a macular eruption which becomes purpuric.

**Etiology**—This disease was first found in the western states of North America but it has spread to the western provinces of Canada and farther afield where the wood tick or *Dermacentor andersoni (tenustus)* abounds. This is the sole method of transmission of the virus which is a Rickettsia named by Wolbach the *Dermacentrozetes rickettsii*. It is similar to the *Rickettsia prowazekii* except that it invades and grows in the nuclei of cells whereas the latter remains in the cytoplasm. This virus is transmitted from one generation of ticks to another and man is not a necessary intermediate host. The disease can be readily duplicated in the monkey rabbit and guinea pig.

**Symptoms and Signs**—The incubation period is from four to eight days and the portal of entry is through the skin. There may be slight prodromal symptoms such as malaise anorexia and chilliness but the real onset is sudden with a chill and pyrexia. There are severe muscle bone and joint pains particularly in the back and legs with intense headache. The face and conjunctivae are injected and there is photophobia. The body temperature is high usually between 104° F and 105° F although it has been reported as high as 107° F. It reaches its maximum during the second week. There are a tachycardia and tachypnea in excess of that expected with the pyrexia the pulse is small and weak and the respirations are shallow.

On the third to fifth day of the disease a rash appears first upon the wrists ankles and back and extends over the arms legs chest abdomen and forehead. It may also appear on the mucous membranes of the mouth and pharynx. It is a rosy macular eruption (2 to 5 mm.) not palpable and disappearing on pressure at first but after a few days it changes to a purpuric or petechial character and at this time cutaneous and subcutaneous hemorrhages

may develop. As the days pass, the rash becomes more extensive and tends to be confluent in the more severe cases. In the milder ones it remains discrete and produces a mottled appearance. Thrombosis of the cutaneous vessels causes the skin to assume a dark purplish to bluish color in areas where the skin is delicate. There may also be necrotic areas in the skin of the fingers, toes, ears, scrotum, prepuce, vulva, and the mucous membrane of the uvula and soft palate. Insomnia, restlessness, delirium and hyperesthesia are distressing symptoms. In the most severe cases convulsions, hypertonia, even to opisthotonos, and coma may occur.

The spleen is enlarged and palpable, and there is usually a slight leucocytosis rarely above 12 000 per cu mm. Anemia occurs but the erythrocytes seldom number less than 3 000 000.

**Pathological Anatomy**—The essential lesion in this disease is found in the blood vessels where there is an endangitis leading to thrombosis which is accountable for the hemorrhagic and necrotic lesions of the skin. Hemorrhages also occur in the testicle and ovary but not in the other viscera. Microscopically there is proliferation of the endothelium and surrounding the vessels there is a good deal of infiltration and the Rickettsia are found in the endothelial and medial cells. Pneumonia is the principal visceral lesion but even this is not common.



Fig 489—Rocky Mountain fever showing characteristic eruption. (Courtesy of Dr John J Sippy. From Sutton and Sutton. *Diseases of the Skin*.)

**Diagnosis**—The close similarity of this disease to typhus fever makes its differentiation obviously important (see page 1353). Other diseases which it may resemble are typhoid fever, cerebrospinal fever, and measles. The rose spots of typhoid fever are palpable while the slow onset, leucopenia, Widal reaction and positive blood culture soon clarify the diagnosis. In the early stages the rash may closely imitate that of measles and although there is no coryza, the photophobia may lead to confusion but the absence of Koplik's spots and lymphadenopathy and the distribution of the rash makes the distinction of these diseases comparatively easy. However when a case of Rocky Mountain fever is first seen in the second week and there are pronounced nervous symptoms it may be difficult to distinguish it from meningococcal meningitis. A lumbar puncture will give positive evidence.

**Course and Prognosis**—The disease usually runs its course in three weeks and the pyrexia terminates by lysis with this there is a rapid improvement,



and if the rash has been pronounced, desquamation occurs. The severity of the case is not in proportion to the intensity of the rash, but rather is directly indicated by the tachycardia and tachypnea. Death usually occurs between the eleventh and seventeenth days. The mortality rate varies greatly in different regions from about 4 per cent in Idaho to nearly 90 per cent in the Beet Root valley of Montana while in the eastern portion of the same state it is about 15 per cent. In children the mortality is quite low but increases with each decade.

**Treatment—Prophylaxis**—As the disease is conveyed by the wood tick it occurs in areas and during the period of the year (March to June inclusive) when this insect is active. Therefore the control of the disease is the extermination when possible of the vector. This is best done by destroying small animals which harbor the larvae, and by dipping cattle so infested. The cultivation of land usually eradicates the source but it continues in waste spaces and on the range. A protective vaccine is now available and its value has definitely been demonstrated in that it protects against less virulent strains and lessens the severity of the more virulent.

**Specific**—Treatment of individual cases is upon symptomatic lines as there are no proved specific measures although a rabbit anti serum has been produced which seems encouraging as is para amino benzoic acid. Many drugs have been used without benefit. A nutritious diet hydrotherapy and plenty of fluids as in all infectious diseases, with good nursing are the best methods of procedure. The restlessness and hyperesthesia require sedatives and it limits morphine as they aggravate the exhaustion which is inherent in all severe infections.

### Relapsing Fever

**Synonyms**—European relapsing fever *spirochæsis febris recurrens* famine fever

**Definition**—It is an acute infectious disease with recurrent periods of pyrexia and afebrile intervals both of which are of six to seven days duration. It is caused by the *Spirillum recurrentis* or Obermeier's spirillum. It occurs in many countries but the spirillum is not always the same. In Europe it is caused by a variant called the *Spiroschandinia recurrentis*, in North America by the *Spirillum novyi* in Africa by the *Spirillum duttoni* and in Asia by the *Spirillum carteri*.

**Etiology**—The spirillum is carried by lice and certain ticks of the genus *Ornithodoros* and these vectors are naturally most prevalent under conditions of filth poverty and famine. The infection is commoner in women and in young adults.

**Symptoms and Signs**—There is a short incubation period of about six days during which there is general malaise and muscle pains. The onset of the paroxysm is explosive with a chill and acute pyrexia. There are also the usual symptoms of an acute infection such as headache general malaise with pains in the back limbs and joints with sometimes nausea and vomiting. The body temperature may reach 105° F to 107° F with a proportionate tachycardia of 140 to 160 per minute. The spleen is enlarged and palpable. A

lower pyrexia continues for six or seven days and then there is a crisis to be followed after a like period by another paroxysm

In addition to these febrile cycles there may appear during the pyrexia cough, laryngitis, glossitis, parotitis, cervical adenitis, arthritis, orchitis, and edema of the feet. Skin eruptions are common, particularly in the severe cases, such as purpura, urticaria, herpes, scarlatinal and morbilliform rashes while in the most severe cases hematemesis, hemoptysis, melena and hematuria may accompany the purpura, all indicating a severe toxic permeability of the capillaries. As the paroxysm reaches a termination, diarrhea and sweating indicate the impending crisis. There is a polymorphonuclear leucocytosis and the parasite is readily found

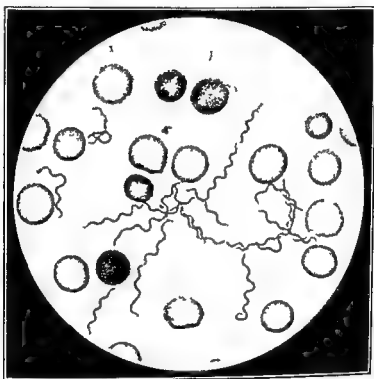


Fig. 490.—Photomicrograph showing *Sprocheta duttoni* in the circulating blood. (Courtesy of Dr. J. L. Todd.)

**Pathological Anatomy**—The pathological anatomy is in no way specific, revealing only an enlarged and septic spleen and cloudy swelling with cellular degeneration no different from any other intense infection.

**Diagnosis**—This disease in the original paroxysm must be differentiated from influenza, pneumonia, malaria, typhus fever, and dengue fever. The direct diagnosis is arrived at by finding the parasites in the circulatory blood. This is done by examining a fresh specimen either by direct or oblique rays. A dried smear stained by a polychrome method will also reveal them.

**Prognosis**—The course is confined to the first paroxysm in a third of the cases. In the others there may be two or more. Most recover from the first, but each succeeding paroxysm takes its toll through exhaustion and toxemia, particularly in the elderly and those reduced by poverty and starvation. The

mortality has varied from one to six per cent in epidemics and this difference depended upon the economic status of the population at the time

Treatment is specific with arsenicals. The spirochetes disappear from the blood and the temperature returns to normal after neoarsphenamine (0.01

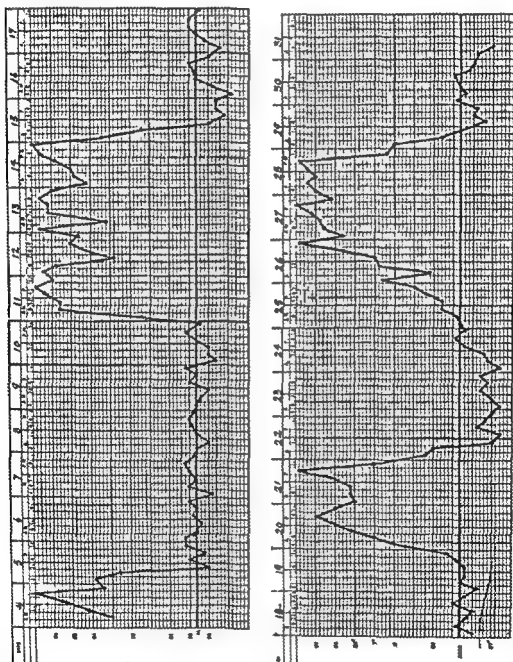


Chart 33331—Temperature chart in a case of relapsing fever

gm per kilogram of body weight) or mapharsen (0.045 gm) intravenously or stovarsol (0.2 gm for 6 doses daily) by mouth. These should be given at the beginning of a paroxysm of fever and not toward the crisis. Penicillin

has also been used with success in a small number of cases (see Chapter XX). If there is a relapse, a repeat dose is usually sufficient to terminate the infection. During convalescence it is important to remain at rest for a week to ten days to avoid recurrences. The ordinary symptomatic treatment of all infections should be followed. It is palliative but in no way curative.

### Plague

**Definition**—Plague is an acute specific infectious disease caused by the *Pasteurella pestis* which is usually conveyed to man by fleas from the rat or other rodents. There are two main types—the *bubonic* in which lymphadenopathy is the principal sign and the *pneumonic* where there is diffuse pneumonia.

**Etiology**—The *Past. pestis* is a bipolar staining, gram negative bacillus which grows readily on ordinary culture media. It infects rats, ground squirrels, guinea pigs, and other small rodents, and the camel. The bacillus may be carried by bedbugs and flies, and in this manner man may occasionally be infected. The principal flea which transmits the disease is the *Xenopsylla cheopis* or rat flea. This parasite conveys the organism from rodent to rodent and thence to man. In certain areas the particular rodent population is always infected to some extent but before an epidemic this incidence rises rapidly and is foretold by then greatly increased death rate. The pneumonic form is transmitted by droplet infection as the sputum contains enormous numbers of the bacilli. All classes, ages, and both sexes are susceptible, but it occurs most commonly among those exposed to fleas. Therefore personal cleanliness is of first importance in escaping infection.

**Symptoms and Signs**—The incubation period is two to seven days, and as already mentioned the portal of entry is through the skin or by inhalation of infected droplets of sputum. The onset is sudden with a chill and pyrexia ranging from 102° F. to 105° F. There are violent headache, vertigo, and great prostration. The face and conjunctivae are injected, but the whole expression is one of great weariness which is characteristic of the disease. There are pronounced tachycardia and tachypnea. The tongue is swollen and much furred, while there may be vomiting at the onset and diarrhea sometimes occurs. The spleen and liver are palpable and there is a polymorphonuclear leucocytosis.

In the bubonic form within twenty-four hours the lymph glands become painful and rapidly enlarge, especially those in the groin, axilla and neck. The first are usually the most prominent. They sometimes suppurate. The mesenteric glands may also be involved and this causes abdominal tenderness. In a few cases the infection seems to gain entrance through the throat, and the glands of the neck are most prominent.

In the pneumonic form the general features are similar but there are cough with hemorrhagic and watery sputum which contains enormous numbers of the bacilli. Signs of bronchopneumonia soon develop and the patches coalesce to form massive areas of consolidation. The incubation period is shorter than in the bubonic type. It should not be confused with a secondary pneumonia.

There is also recognized a *septicemic form* in which there is an overwhelming blood infection. The patient usually dies before either the buboes or pneu-

monia can develop. Quite the opposite to this type is a mild form called *pestis minor* or *ambulatory plague*. All the symptoms are of slight degree, although the buboes may suppurate. The patient frequently continues to be up and about and is a source of danger in spreading the disease, as it is just as infectious as the severer forms.

In the severe cases there may be *petechiae*, *ecchymoses* and hemorrhages from the skin, mucous membranes and kidneys. Occasionally vesicular or pustular eruption occurs, and there may be cutaneous necrosis.

**Pathological Anatomy**—The portal of entry on the skin may sometimes be recognized by a small vesicle. The lymph glands show intense congestion and hemorrhagic edema. Those draining the portal of entry are most severely involved and in the surrounding tissues there is also edema and hemorrhage. There is widespread injury to the vascular endothelium which is productive of hemorrhages into the skin, mucous membranes, spleen, kidneys, meninges and brain. There may also be intense congestion of the respiratory and gastrointestinal tract. In the septicemic form although the lymph glands are not grossly affected, on microscopical examination there are found hemorrhagic extravasations. In the pneumonic form there is an intense inflammatory reaction in the bronchial mucous membrane which extends into the peribronchial and bronchiolar tissues and alveoli. The bronchial and tracheal lymph glands are enlarged although the others may not be.

**Diagnosis**—Plague may be confused with influenzal pneumonia in the pneumonic type or with tularemia, syphilis and acute mononucleosis in the bubonic form. Bacteriological examination of the sputum establishes the diagnosis in the first, but in the mild forms of the bubonic variety the diagnosis may be more difficult. It should always be suspected in areas where plague has ever been and especially in seaports. Absolute proof can be obtained by gland puncture or biopsy and inoculating proper laboratory animals or culture media with the gland juice. The organisms may be recognized in smears from such, but a negative result is not conclusive. In the septicemic cases they may be found in blood smears and blood cultures are always positive and frequently so in other forms.

**Course and Prognosis**—The duration of the disease in those that recover is usually about four to eight days and if a case lasts a week it usually results in recovery. The pneumonic and septicemic cases nearly all end in death within a few days although mild cases of the latter may end in recovery. In bubonic plague the mortality varies in different epidemics from 30 to 90 per cent. Infants and children are less severely affected than adults. With recovery there is a certain degree of immunity which may protect from a second attack or render it quite mild.

**Treatment**—*Prophylaxis* rests to a great extent upon the suppression of the rodent population in infected areas, and the prevention of their transportation by sea. Individual protection depends upon thorough personal cleanliness, wearing rubber gloves when handling infected material and a face mask when attending or nursing pneumonic cases. Antiplague vaccine has been extensively used and appears to produce a moderate immunity for a short indefinite period but will not protect against a massive infection.

The treatment of the individual is the same as that for any acute infection. Hyperpyrexia must be controlled with hydrotherapy. In addition, sulfadiazine should be given in full doses (see Chapter XX). High blood levels should be attained (20 mg per cent) and continued over four to five days and then the amounts should be gradually reduced but continued after the temperature reaches normal. If necessary, it should be given intravenously. This is advisable in severe cases and when the therapy is started late in the disease.

### Q Fever

**Definition**—Q fever is an acute febrile disease which has been identified in the Southwest of the United States and in Australia.

**Etiology**—It was at one time thought to be due to two separate rickettsiae, namely *burneti* in Australia and *diaporica* in the United States which are now believed to be identical. It has not been definitely proved that the vector is the tick, although the organism has been isolated from them. It has occurred in forest workers, slaughter and packing house employees, and train crews in cattle trains. The animals which are most likely to carry the vector are cattle, pigs, and bandicoots (Australia).

**Symptoms and Signs**—The onset is sudden with pyrexia, sometimes chills, nausea, vomiting, headache, and a leucocytosis. General pain in the limbs may be prominent with some stiffness of the neck, severe sweats, and insomnia. There is sometimes cough, which is usually unproductive but may on occasion be accompanied by a small amount of thick, tenacious mucoid sputum, rarely blood tinged. Thoracic pain of a neuralgic rather than pleural type may be present. The physical signs are few or absent except over the lungs where rarely a scattered distribution of rales and changed breath sounds are heard but x-rays commonly reveal a patchy infiltration similar to broncho or atypical pneumonia.

**Diagnosis**—The diagnosis is usually made by recognizing the possibility of such an infection and demonstrating agglutinins to the rickettsia in the blood. The Weil-Felix reaction with proteus brevix is negative.

**Prognosis**—The disease may last for one to two weeks. The mortality varies in different outbreaks from 1 to a per cent.

**Treatment** is symptomatic.

### Bulbs Fever

**Synonyms**—Jone Star fever, Texas tick fever.

An acute febrile disease broke out in those who had been the victims of many tick bites in the Bulbs camp area in Texas. The onset was sudden with chills and pyrexia of 102° to 104° F. The principal symptoms were prostration, anorexia, weakness, and weight loss, while the signs included a maculopapular rash on the trunk, lymphadenopathy, and a leucopenia. The blood cultures were always negative as were serum reactions. There is still some controversy as to whether this disease is caused by a virus or a rickettsia.

The duration of the disease is 4 to 14 days and the death rate almost nil. The treatment is symptomatic.

### Colorado Tick Fever

The Colorado tick fever is a milder febrile disease closely resembling the Texas type. It is transmitted by tick bites and exhibits general myalgia, photophobia, leucopenia, negative Weil-Felix reaction and a definite remittent interval. The cause has not been identified although the tick bite may develop into an indolent ulcer.

The prognosis is good and the treatment symptomatic.

### Rickettsialpox

In 1946 a fairly localized outbreak of an unclassified acute infectious disease was reported by the New York City Health Department.

The onset occurred with a primary papular lesion. This was roundish and firm without surrounding erythema. It gradually grew in size, developed a central vesicle which was deep and firm. The lesion eventually became a black eschar.

About one week after the start of the initial lesion there was a sudden onset of chills, fever, headache, sweats and prostration. At this time a discrete maculopapular erythematous rash developed. In a few days a vesicle appeared which shortly dried leaving a black crust. There was usually a leucopenia. The Weil-Felix reaction was negative. Rickettsial strains were isolated from the blood of several patients and from pooled blood of rodent mites, *Blodermomyssus sanguineus*.

The disease ran a comparatively mild course. There were no deaths and the treatment was symptomatic.

### Swineherd's Disease

**Synonyms**—*Maladie de Bouchet*, pseudotuberculous meningitis.

**Definition**—Bouchet in 1914 described in Haut Savoie an acute febrile disease conveyed apparently from swine to man characterized by a preliminary typhoidal phase of headache, malaise, skeletal pains and abdominal symptoms. A period of remission is followed by a second phase with meningeal symptoms.

**Etiology**—Bacteriological examinations of the blood have been negative but the virus is uniformly in the blood and passes through an L candle. The urine is likewise infective in a large percentage of cases while the cerebrospinal fluid is less frequently so. It has been transferred from man to man through twenty-one passages by plasma inoculation but apparently does not occur by case to case infection. The serum of convalescent patients neutralizes the virus. The manner of its conveyance from pigs to man is unknown but the louse is suspected. There is strong evidence that it is due to a filterable virus. The disease is supposed to affect young pigs one to two months of age sometimes in epidemic form producing convulsions. It lasts about fourteen days and has a low mortality.

**Incubation Period**—The incubation period is about twelve days in the experimental disease.

**Onset and Course**—The onset is fairly acute with pyrexia, headache, muscle pains and prostration soon followed by vomiting, diarrhea and meteorism.

and occasionally melena. This preliminary state lasts about four days when there is a remission to be followed in about forty eight hours by a second rise of temperature and signs of meningeal irritation. This phase is not constant. Conjunctivitis is common as is a nonhemorrhagic macular or maculopapular rash on the abdomen and inner aspects of the thighs just before the remission. There is a polymorphonuclear leucocytosis. In the second phase the cerebrospinal fluid is under pressure and several hundred lymphocytes per cubic millimeter are present.

The disease terminates in a crisis or rapid lysis in about nine days and is very seldom fatal.

The treatment is symptomatic.

### DISEASES CARRIED BY BLOOD SUCKING INSECTS

In the previous section were described diseases in which certain insects transmitted the virus from lower animals to man, or from man to man, without, however, necessarily directly inoculating the new host. Blood sucking insects, on the other hand, introduce the virus into the human blood stream through their capacity of penetrating the skin and injecting the virus. Diseases so inoculated do not necessarily pass through an intermediate host except the insect. There is also another important difference, whereas the biting insects are usually associated with filth and body uncleanness, the blood sucking insects are dependent more upon a neglect of community rather than personal hygiene.

#### Malarial Fevers

**Synonyms**—Malaria, ague, chills and fever.

**Definition**—Malaria is a specific infectious disease having an acute onset with chills and pyrexia which recur at regular intervals, or the pyrexia is continuous with marked remissions. It may assume a rapidly fatal or pernicious form.

**Incidence**—Malaria was common seventy five to one hundred years ago in European countries such as Italy, France, Germany, and England and throughout the northern United States. It is now chiefly confined to tropical and subtropical countries being prevalent in India, Burma, Africa, China, Russia, tropical Australia and the Indies, the southern portions of the United States and Central and South America. In those areas where there is a heavy rainfall it is particularly common and from time to time the mortality and morbidity are extremely high.

**Etiology**—Although there are five or six clinical varieties of this infection, with considerable overlapping and divergence of signs and symptoms, there are really only three varieties of this parasite each one of which is usually accompanied by a rather clear cut clinical picture but their combination may lead to confusion in the correlation of the clinical pattern and the etiological agent.

- (a) *Tertian malaria* due to *Plasmodium vivax* and *Plasmodium ovale*
- (b) *Quartan malaria* due to the *Plasmodium malariae*
- (c) *Aestival-autumnal malaria* due to the *Plasmodium falciparum*



It is usual to refer to these several plasmodia as the tertian, quartan, or actino autumnal parasites. They belong to the division Protozoa, class Sporozoa, order Haemosporidia, and Genus Plasmodium. They are all closely related but have certain distinguishing morphological characteristics which can usually be recognized by those who have expert knowledge.

The parasite is inoculated through the skin by the female mosquito of the genus Anopheles. Man acts as the intermediary host while the mosquito is



FIG 491.—*Plasmodium* (Tertian plasmodium). 1 Young form of the so-called tertian parasite  $\times 100$ . 2 Quarter grown parasite  $\times 100$ . 3 Half grown parasite  $\times 1500$ . 4 Three quarters grown parasite  $\times 1500$ . (Photomicrographs made at the U. S. Army Medical Museum.)

the definite host. All of these parasites go through a similar cycle in man where they reach maturity and reproduce. After inoculation they appear first attached to the erythrocyte as a small yellowish protoplasmic mass with a nucleus rich in chromatin. These are called the merozoites. They are about  $\frac{1}{10}$  to  $\frac{1}{20}$  the size of an erythrocyte and soon penetrate it. The tertian is

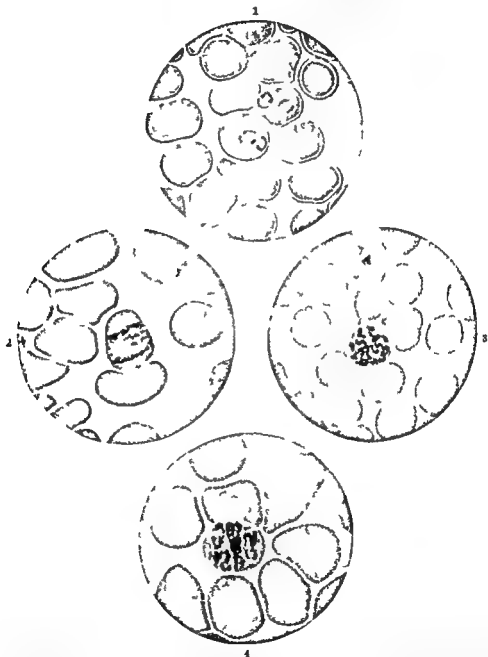


Fig. 492—*Plasmodium malariae* (Quartan plasmodium). 1. Young parasites the so-called ring forms.  $\times 100$ . 2. Half grown parasite the so-called band form.  $\times 1500$ . 3. Three quarters grown parasite.  $\times 100$ . 4. Large band form.  $\times 1500$ . (Photomicrographs made at the U. S. Army Medical Museum.)

irregular and may be ameboid. When stained within the cell they have a general appearance of a silver ring. They gradually enlarge and brownish pigment appears within them in about 12 to 15 hours. This can be recognized

in fresh specimens and appears motile. It is apparently obtained from the hemoglobin. This pigment increases in amount with the parasitic growth, and the nucleus at the same time becomes polymorphous and begins to show segmentation. The tertian parasite grows more quickly than the quartan and at the end of 30 to 70 hours, depending upon the variety, it occupies the area of the whole erythrocyte which now may appear as a thin envelope. The divisions of the parasite become complete, each containing a small nucleus.

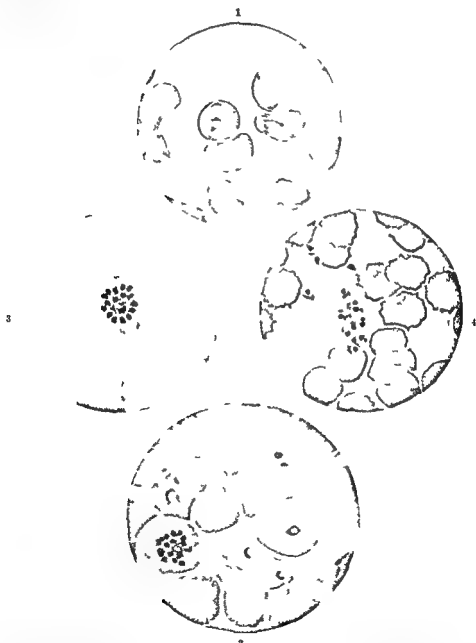


Fig 493.—*Plasmodium falciparum*. (Acute autumnal plasmodium.) 1 Ring parasite X1800. 2 Sporulating parasite and several young ring forms X1800. 3 Sporulating parasite X1800. 4 Pores or merozoites X1500. (Photomicrographs made at the U. S. Army Medical Museum.)

These are called rosettes and number 8 to 32 merozoites. The envelope ruptures and these are set free in the blood stream, each in time attaches itself to another erythrocyte, and so the reproduction continues. If it were not for the phagocytic power of the leucocytes and the cells of the reticulo endothelial



Fig 494—*Plasmodium falciparum*. 1 Phagocyte containing gametocytes. 2 The male gamete or crescent (microgametocyte) X1500. 3 The female crescent or gamete (macrogametocyte) X1500. 4 The female crescent or gamete (macrogametocyte) X1500. (Photomicrograph of the U S Army Medical Museum)

system, they would soon multiply to enormous numbers. The only ones that escape destruction are those that become attached to and invade an erythrocyte. The malarial parasite does not choose to remain in the circulating blood if avoidable, but would rather rest in the spleen bone marrow or liver, on

account of the slow circulation and fortunately this is where the reticulo endothelial system is most abundant. This asexual cycle usually occupies a consistent time period for the various parasites: the tertian, 48 hours; the quartan, 72 hours; and the aestivo autumnal, 24 to 48 hours. After a few days sexual forms make their appearance, and the male and female can be differentiated by those with experience. The sexual forms are called gametocytes or gametes. In the tertian and quartan malarias these are rounded or oval

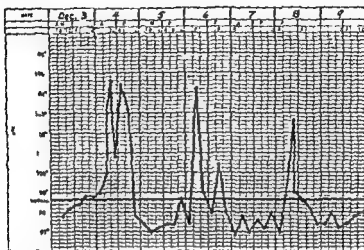


Chart XXXVII—Temperature chart of simple tertian malaria

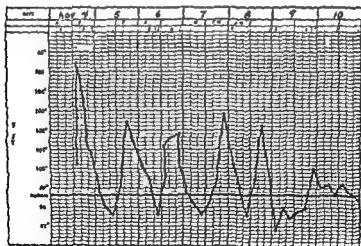


Chart XXXVIII—Temperature chart of a double tertian infection, showing quotidian type of temperature

ameboid and irregular while in the aestivo autumnal the ameboid movement and therefore the irregularity is very slight and they are usually oval or crescentric. They live for two to three weeks but are constantly being replaced.

When the *Anopheles* sucks blood containing gametes into its stomach the male (microgametocyte) produces long flagellae which break off and invade the female (macrogametocyte) which is then fertilized and the cycle of reproduction is started. The fertilized zygote now progresses by ameboid move-

ment through the stomach wall to its outer surface in the abdominal cavity. It rapidly grows in size and at the end of 15 to 25 days is a large oocyst containing numerous spindle shaped bodies which are a small protoplasmic

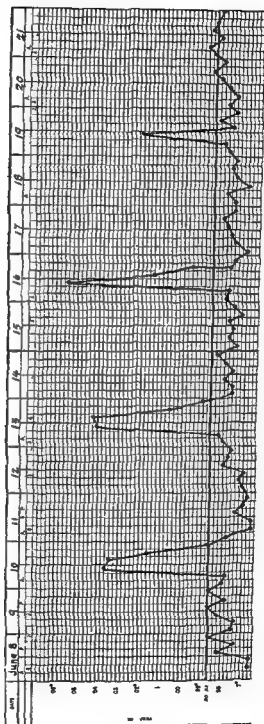


Chart XXV.—Temperature chart of quarian malaria

mass and a nucleus. The oocyst ruptures and the young parasites (sporozoites) are set free. Some of these reach the salivary glands and are inoculated into the next victim bitten by the mosquito and so the cycle continues from man to mosquito, and from mosquito to man.

**Symptoms and Signs**—Malarial fevers may be generally classed in two groups: (a) those which have regular remittent bouts of pyrexia and (b) those where the pyrexia is continuous over irregular periods of time

The first group has given to these fevers a number of synonyms such as ague, chills and fever, quotidian tertian, and quartan malaria. The quotidian type is that in which chills occur every day and is caused by a double infection of the tertian parasite. In tertian malaria the chill occurs every other day and in the quartan variety two days elapse between the chills. A double quartan infection could produce a chill for two days in succession and then there would be a free day, while if there is a triple infection chills will occur daily as in the quotidian or double tertian type.

The character of the chills is the same in all varieties of this infection. There are certain prodromata such as headache, lassitude, yawning and sometimes nausea and vomiting. Shortly after these symptoms have appeared the body temperature begins to rise. The patient may be quite unconscious of this but soon he begins to shiver and before long a violent rigor ensues. He feels intensely cold; the skin and mucous membranes are pale and bluish, and the surface temperature is lowered. Inspection of the capillaries of the nail bed under the microscope at this time shows these to be contracted and the blood flow extremely sluggish. The body temperature by rectum is greatly elevated, at times to 106° F. There may be delirium and in children convulsions. This stage may last from a few minutes to an hour or more to be followed by a sense of intense heat; the body surface is then erythematous and dry. Whereas the pulse in the initial stage was small, it is now full and bounding. There is great thirst, headache and active delirium. The capillaries in the nail bed are dilated and the blood flow is extremely rapid. In from thirty minutes to several hours perspiration begins which soon progresses to a drenching sweat. The patient is now much relieved although exhausted, and as a rule passes into a deep sleep. This is the description of a moderately severe paroxysm. All cases do not necessarily conform to this general description as there are variations in degree rather than in sequence. The whole paroxysm usually occupies from 8 to 12 hours and recurs with remarkable regularity at the same hour of the day during the height of the disease but as the infection is being overcome the intervals may become longer.

Herpes labialis is common. The liver may be enlarged and the spleen is palpable but during the intervals it may not be felt.

In the second form there is a more continuous remittent fever and chills do not occur with any regularity although they may be present at the onset. This type may be caused either by the tertian or the quartan parasite but it is most common when the infection is due to the *Plasmodium falciparum* or aestivo autumnal parasite which means "summer" and "autumn" when the disease is most common. When due to the last parasite the onset of the pyrexia is as a rule gradual somewhat like typhoid fever, and chills are uncommon. It is in this type that the so-called 'pernicious' malaria occurs the name being applied to very severe forms which are probably due either

ment through the stomach wall to its outer surface in the abdominal cavity. It rapidly grows in size and at the end of 15 to 25 days is a large oocyst containing numerous spindle shaped bodies which are a small protoplasmic

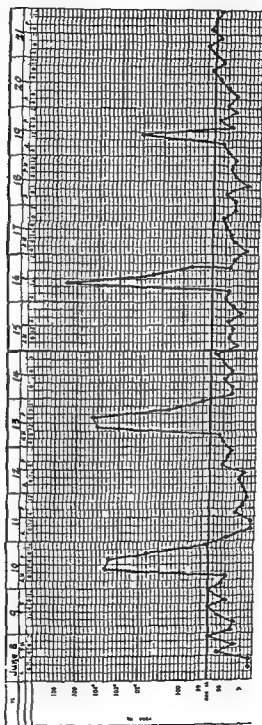


Chart XXXIX.—Temperature chart of quarian malaria.

mass and a nucleus. The oocyst ruptures and the young parasites (sporozoites) are set free. Some of these reach the salivary glands and are inoculated into the next victim bitten by the mosquito and so the cycle continues from man to mosquito, and from mosquito to man.



**Symptoms and Signs**—Malarial fevers may be generally classed in two groups (a) those which have regular remittent bouts of pyrexia and (b) those where the pyrexia is continuous over irregular periods of time

The first group has given to these fevers a number of synonyms such as *ague*, *chills* and *fever*, *quotidian*, *tertian*, and *quartan malaria*. The *quotidian* type is that in which chills occur every day and is caused by a double infection of the *tertian* parasite. In *tertian malaria* the chill occurs every other day, and in the *quartan* variety two days elapse between the chills. A double *quartan* infection could produce a chill for two days in succession and then there would be a free day while if there is a triple infection chills will occur daily as in the *quotidian* or *double tertian* type.

The character of the chills is the same in all varieties of this infection. There are certain prodromata such as headache, lassitude, yawning and sometimes nausea and vomiting. Shortly after these symptoms have appeared the body temperature begins to rise. The patient may be quite unconscious of this but soon he begins to shiver and before long a violent rigor ensues. He feels intensely cold, the skin and mucous membranes are pale and bluish and the surface temperature is lowered. Inspection of the capillaries of the nail bed under the microscope at this time shows these to be contracted and the blood flow extremely sluggish. The body temperature by rectum is greatly elevated at times to  $106^{\circ}\text{F}$ . There may be delirium and in children convulsions. This stage may last from a few minutes to an hour or more to be followed by a sense of intense heat, the body surface is then erythematous and dry. Whereas the pulse in the initial stage was small it is now full and bounding. There is great thirst, headache and active delirium. The capillaries in the nail bed are dilated and the blood flow is extremely rapid. In from thirty minutes to several hours perspiration begins which soon progresses to a drenching sweat. The patient is now much relieved although exhausted and as a rule passes into a deep sleep. This is the description of a moderately severe paroxysm. All cases do not necessarily conform to this general description as there are variations in degree rather than in sequence. The whole paroxysm usually occupies from 8 to 12 hours and recurs with remarkable regularity at the same hour of the day during the height of the disease but as the infection is being overcome the intervals may become longer.

*Herpes labialis* is common. The liver may be enlarged and the spleen is palpable but during the intervals it may not be felt.

In the second form there is a more continuous remittent fever and chills do not occur with any regularity although they may be present at the onset. This type may be caused either by the *tertian* or the *quartan* parasite but it is most common when the infection is due to the *Plasmodium falciparum* or *aestivo autumnal* parasite which means summer and autumn when the disease is most common. When due to the last parasite the onset of the pyrexia is as a rule gradual somewhat like typhoid fever and chills are uncommon. It is in this type that the so-called *pernicious malaria* occurs the name being applied to very severe forms which are probably due either

to a lack of resistance of the host or to the concentration of the parasites in vital areas. It is customary to recognize three forms

(a) **Comatose Type**—This is distinguished by severe symptoms in the central nervous system, especially violent delirium and coma. It is supposed to be due to the cerebral capillaries being blocked by vast numbers of the parasites, in other words, they produce capillary thrombi in the cerebrum.

(b) **Algid Type**—Here gastrointestinal symptoms dominate the clinical picture. There is great prostration and asthenia, vomiting and diarrhea with melena being the chief features. These symptoms are supposed to be due to the capillaries of the gastrointestinal tract being affected by the parasite in the same manner as the cerebral vessels are affected in the comatose variety.

(c) **Hemorrhagic Type**—In malaria, hemoglobinuria is not an unusual event due to the destruction of enormous numbers of erythrocytes, but in this type there is gross interference with renal function. The urine becomes darker and darker, although it may return to a normal color for a few days, but the abnormal appearance comes back with each succeeding bout of pyrexia. There may also be suppression of urine. Chills occur and are extremely violent although the temperature may not be high. Anemia soon is conspicuous and there is a rapid loss of weight.

In all severe malarial infections but particularly in the aestivo autumnal type, what is known as "malarial cachexia" may occur. There are slight fever, anemia, dyspnea particularly on exertion, edema, and hemorrhages into the skin and retina and the spleen is conspicuously enlarged. With recurring attacks this condition is not unusual. The anemia may be below 2,000,000 erythrocytes and normoblasts and spindle cells are frequently found. A leucocytosis, although not usual, may occur during very severe paroxysms and may be as high as 20,000 due to an increase of the granulocytes and the large mononuclear cells.

**Pathological Anatomy**—The most conspicuous anatomical change in malaria is found in the spleen which in fatal cases is enormously enlarged. It is smooth and the capsule is thin. In color it may be greyish to an absolute black. The pulp is soft and the malpighian bodies are easily seen. On microscopic examination the principal characteristic is the thickening and the swelling of the blood vessels which are often obstructed by massive collections of the parasites which are not only free in the lumen of the vessels but also are found in large numbers in the endothelial cells of the blood vessels and those of the reticulo endothelial system. The liver is also enlarged and similar blockage of the small vessels and the endothelial and reticulo endothelial cells are gorged with parasites. There is great congestion of the organ and deposits of pigment may be readily seen. The kidneys, brain and bone marrow are similarly affected, in fact the common anatomical change in all malarial lesions is the obstruction of the capillaries by the malarial parasites and their presence within the cells of the reticulo endothelial system and the endothelial cells of the blood vessels even in areas where the reticulo endothelial system is not supposed to be abundant. The larger vessels may be affected in this manner as well as the smaller ones.

**Course**—All patients who have had malaria are subject to relapses. It is difficult, when they are living in a malarial district, to be certain whether these relapses are not reinfections, but in patients who have removed to an environment where malaria as a local disease is uncommon, relapses may occur after several years. Without treatment the tertian and quartan types frequently recover spontaneously and practically always do if sufficiently treated but if the therapy is not continued to a conclusion, relapses are common when it is stopped. Aestivo autumnal malaria is more persistent than the other two and does not recover spontaneously as frequently, but with treatment relapses are not so common. The clinical features of a relapse are the same as in the original infection. The secondary lesions or complications of malaria are attributable to the changes in the vascular system, and may be extremely numerous if all those reported are taken into consideration. They are found particularly in the central nervous and hemopoietic systems and are represented by paraplegia, hemiplegia, neuritis, ataxia, disseminated sclerosis and anemia.

**Diagnosis**—There is usually but little difficulty in the diagnosis of an acute case of malaria. It is particularly to be differentiated from other tropical infectious diseases such as yellow fever, relapsing fever and dengue, but in addition it may be confused with bacillary dysentery, septicemias of various types, typhoid fever and acute bacterial endocarditis. The identification of the parasite in the circulating blood or by splenic puncture makes the diagnosis absolute. If this confirmation cannot be obtained, it is often necessary to have recourse to the therapeutic test with quinine. It is of more negative than positive value in that if the pyrexia does not disappear when the patient is taking quinine it is of more significance than if it does, which would not necessarily eliminate malaria. Every effort should be made to detect the parasites before quinine is given because once this therapy has been started it is difficult to be certain whether the continued absence of the parasite is due to the quinine or whether some other febrile disease is present. It must be appreciated that all cases of malaria do not necessarily follow the classical clinical description. This is particularly so when due to the *P. falciparum* when a great variety of clinical patterns may be encountered which may simulate practically any febrile illness. It may be confused with subacute bacterial endocarditis,iliary tuberculosis, amebic abscess of the liver, typhoid fever etc.

**Prognosis**—If treatment is started early and continued thoroughly in a mild or moderate case of malaria recovery occurs in approximately 100 per cent of the cases. In tertian and quartan malaria the mortality is low even in untreated cases but in the aestivo autumnal variety if the treatment is insufficient or is long delayed the mortality rises rapidly in direct ratio to these two factors. About 50 per cent of the deaths occur in the comatose type of pernicious malaria and the rest are accounted for by the algid and hemorrhagic types and malarial cachexia due to all types.

**Treatment**—**Prophylaxis**—As malaria is spread by the *Anopheles* mosquito the principal method of prophylaxis is the extermination of this insect by drainage of all stagnant waters or if this is impracticable by covering them with oil so as to prevent the maturation of the larvae. When extensive

operations of this manner are indicated, it may be impracticable therefore means to kill the larvae are used. For this purpose an oily substance called "Malaria-riol," which is effective in a high dilution when sprayed on the water, or Paris green may be used. This is a public health problem in which, however, the physician should take an active part in education and propaganda. In addition all houses should be screened, and if necessary bed nets should be used. In latent cases treatment should be continued as these although not suffering clinically themselves are a source of re-infecting the mosquito which can then transmit the disease to a susceptible individual. This is particularly important in the itinerant population, as a vagabond with latent malaria may re-infect districts in which this disease has been exterminated.

The principal drugs used in the treatment of malaria are quinine and some of its alkaloids and several synthetic antimalarial agents. The latter are atabrin hydrochloride (mepherine hydrochloride) and atabrin musonate (mepherine methane sulphonate). The latter is for parenteral use.

There is not known at present any drug which can affect the sporozoite and therefore be a true causal prophylactic in therapeutic doses. In the schizont stage both the drugs mentioned above are effective and therefore can be used to control the acute malarial attack. Quinine is probably the most effective. In the gametocyte stage quinine is the more effective particularly for *P. malar* and *P. malariae* which produce benign tertian and quartan malaria but has little if any action on the crescents of *P. falciparum*. Therefore being a poor gametocide it has little value as a sterilizing agent in the carrier state. The same may be said of atabrin however it has certain advantages as follows: 1 It can be taken easily and without discomfort by mouth. 2 There are few side effects. 3 Bilial water fever is not a contraindication. 4 It is secreted more slowly than quinine. On the other hand it is in some ways inferior to quinine: 1 Its initial action is slower. 2 It may produce a yellow discoloration (not jaundice) of the skin. 3 Rarely may produce a transient confusional psychosis.

**Suppression Methods**—During war when troops *en masse* are exposed to and contract malaria it has become customary to suppress the active symptoms by the use of quinine or atabrin (mepherine). This therapy should be started before entering the malarial region and continued. Atabrin has been chiefly employed. There is some difference of opinion as to the dosage of atabrin for this purpose. Some advise 0.1 gm. on four days a week some 0.2 gm. twice a week others 0.06 gm. six days a week and still others 0.05 gm. every day. It would appear that these differences of opinion are immaterial and that the principal point to be borne in mind is a constant level in the blood therefore frequent use of small amounts is better than larger amounts at intervals. It will be noted that these methods are not strictly prophylactic but suppressive, in other words they inhibit the symptoms of malaria becoming incapacitating and do not necessarily eradicate the plasmodia.

**Active Methods**—The active treatment of malaria in the individual rests upon the continuous use of quinine in proper quantities until the disease is cured. In the acute stages 30 grains (3 doses of 10 grains each) of quinine sulfate should be taken daily for at least four days. This amount is a rule is sufficient to prevent paroxysms but not to effect a complete cure. For the next three months 10 grains a day should be taken without intermission. In

persons who have not had acute paroxysms but who are infected, only this portion of the treatment is necessary. The dosage for children is proportionate and is roughly as follows: under the first year,  $\frac{1}{2}$  grain; first year, 1 grain; second year, 2 grains; third and fourth years, 3 grains; fifth, sixth and seventh years, 4 grains; eighth, ninth and tenth years, 6 grains; eleventh, twelfth

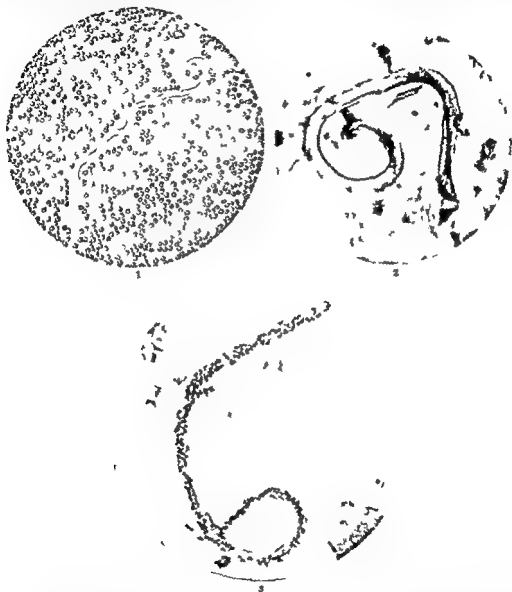


Fig. 495.—*Filicilia bancrofti*. (1) *Filicilia bancrofti* containing within its sheath. (2) *Filicilia bancrofti* after emerging from the sheath. (3) *Filicilia bancrofti* after emerging from the sheath. (Photomicrographs made at the U. S. Army Medical Museum.)

thirteenth and fourteenth years, 8 grains; fifteenth year and over, 10 grains, all three times a day. Although it is quite clear that all patients do not require the same amount of quinine over the same period of time to effect a cure, it is impossible to forecast this in any individual case. Therefore it is best to be on the side of safety.

Other salts of quinine have been used but have no advantage over the sulfate which is undoubtedly the most effective. In emergencies quinine may be given intravenously, but this method is not as efficacious in the long run as when taken orally. A synthetic quinoline called "Plasmochin" has been used. There is no doubt that it can cure malaria, but it is more common to use it in a combined tablet containing  $\frac{1}{6}$  grain plasmochin and 2 grains quinine. Two such tablets are taken three times daily for a week with an interval of four to five days when the course is repeated, and so is carried on for five or six times. That it has any particular advantage over quinine in the majority of cases is not proved. It is a boon to those who have an idiosyncrasy for the latter. Atabrin kills the tertian and quartan plasmodia but not the gametocytes of the aestivo autumnal plasmodia. Therefore to destroy these it must be combined with or followed by plasmochin.

During World War II extensive and intensive work was done on newer chemotherapeutic antimalarial drugs. This was of particular importance on account of the scarcity of quinine. It also stimulated a more thorough investigation of atabrine both as a suppressive and as an agent in the treatment of the acute attacks and relapses. Out of the former work chloroquine 7-chloro-4-(4-diethylamino-1-methylbutylamino) quinoline was found in experimental animals to be much more effective than either quinine or atabrine. Although it will not prevent an infection, it will terminate an acute attack and is a good suppressive. As a cure the combination of a plasmochin like substance (6-methoxy-8-15-isopropylamino-methylamino quinoline) combined with quinine has given great promise. These compounds are not now readily available, so time will prove them worth.

The general treatment of malaria is the same as in any other acute infectious disease. The complications usually recover spontaneously or if not nothing can be done for them but what would be indicated in a symptomatic form. Hemoglobinuria is still the subject of debate as to its proper treatment. It is claimed by some that quinine aggravates this condition, while there are others who are strong advocates for its use. It is true that quinine may produce hemolysis if taken in sufficiently large quantities or in those who are peculiarly susceptible. Therefore quinine should be given in smaller amounts than outlined above until the hemoglobinuria has disappeared.

### Filariasis

**Definition**—Filariasis is a specific disease caused by the invasion of nematode worms called filariae. These worms enter the blood stream as embryonic forms called microfilariae transmitted by the mosquito. Of the four species found in man there is only one, namely *Filaria (Wuchereria) bancrofti*, which causes important pathological lesions. The others *Filaria loa*, *Filaria ozzardi*, and *Ancanthocheilonema perstans* are of little importance as only one of them the *Filaria loa* sometimes may produce disabling conditions. It is called the "eye worm" of West Africa and causes calabar swellings. The principal lesion produced by the *Filaria bancrofti* is a blockage of the lymphatic channels leading to a lymphatic edema (*elephantiasis*) or chylous transudate.

**Distribution**—This infection has a wide geographical distribution. It is still found in the southern states of the United States, but is much more prevalent in certain parts of the West Indies, Africa, the East Indies and the Pacific Islands. It is also found in northern Australia and has a wide distribution in northern South America.

**Etiology**—The disease is caused by the *Filaria bancrofti* which is a nematode worm. In its adult form the female measures 50 to 100 mm in length, and 0.2 to 0.3 mm in width. It has a simple head with two rows of small papillae. It looks like a thin piece of wet catgut. The uterus which consists of two tubes occupies the greater part of the body, the eggs being formed in the posterior portion. As they proceed forward to the vagina they grow rapidly and are discharged as microfilariae, the chorionic membrane forming an enveloping sheath. The microfilariae measure about 0.103 mm. The infection is transmitted from man to man by means of the mosquito, two varieties being chiefly accountable, namely the *Aedes triseriatus* in Polynesia, and the *Culex fatigans* in other countries. The microfilariae are found free in the circulating blood, and when the mosquito sucks blood from an infected person the microfilariae reach the mosquito's stomach where they shed their sheath and find their way into the thorax, becoming imbedded in the muscle fibers where they undergo considerable development, and after about twenty-one days they migrate to the head and lodge in the proboscis. When a mosquito attacks man, the parasites are lodged under the skin, or may even penetrate into the blood and lymphatic channels. Many of these parasites may remain about the portal of entry. They are carried by the lymphatic and blood streams to far distant parts of the host and have a particular predilection for lymphatic channels and lymphatic glands. They also have a tendency to collect in groups in localized areas of tissues.

Except in Polynesia the *Filaria bancrofti* shows a definite periodicity. The reason the Polynesian strain does not do this is unknown. Although occasionally a microfilaria may be found in the blood stream during the day, it is after 6:00 P.M. that they begin to increase in numbers and between 10:00 P.M. and 2:00 A.M. that they reach their maximum concentration and then gradually diminish in numbers again. It has been suggested by Lane that this is due to a cyclical birth of microfilariae from the parent female.

**Symptoms**—All patients infected with filariae do not necessarily suffer any inconvenience. The association of these parasites with the lymphatic tissue however may produce a variety of conditions in different individuals. There may be lymphangitis, adenitis, lymphedema or elephantiasis, lymphatic varicosities, enlargement of the spermatic cord and epididymis, chyluria and chylous exudate into the pleura, peritoneum and pericardium, or cysts may be formed in the skin, glands and the breasts or other tissues. The most characteristic features apart from the chyliform serous transudates are filarial lymphangitis and elephantiasis.

### *Filarial Lymphangitis*

This condition is ushered in by an acute pain in the limb or in superficial glands. The pain is widely distributed and indefinite in localization but may

be more severe in one place than in another. In twenty four to forty eight hours there is a chill with pyrexia, the latter continuing for about three days. There are the usual signs of infection accompanying it, such as headache, malaise, nausea, and vomiting. Shortly following the chill, streaks or patches of erythema may appear on the skin outlining the superficial lymphatics, or a confluent area of lymphatic inflammation which may cover quite a large area. It is exquisitely tender and painful. The erythema shades off into the surrounding skin and has not a clear cut margin as in erysipelas. These attacks vary greatly in intensity, some are mild and fleeting, while others are most intense. In the latter there is sweating, great prostration, malaise and anorexia. In a few days the whole inflammatory action seems to subside. Recrudescences occur about every three weeks in most cases, but in some there may be an interval of many months. Although the reaction usually recurs in the same place in each individual, this is not necessarily so. Secondary bacterial infections are not uncommon and in such the general systemic reaction is relatively severe compared to the local lymphangitis.

### Elephantiasis

Elephantiasis is a condition of lymphedema. It may occur following filarial lymphangitis or independent thereof (see above). At first there is an edema which pits on pressure but as time passes the swelling becomes more and more brawny and indurated. This is not due to the lymphatic stasis, but results from fibrosis secondary to bacterial infection. Elephantiasis usually occurs in the legs, scrotum penis, and vulva and may also be found in other parts of the body. When there is elephantiasis with recurring attacks of lymphangitis it is commonly called "elephantoid fever". In such cases the part continues to enlarge, while in ordinary filarial lymphangitis the edematous area returns to its normal size.

Abscesses in the skin or elephantoid tissue are quite common and are caused by pyogenic infection particularly the streptococcus and staphylococcus. When these abscesses are opened, these organisms can be recovered in smears and culture. There is however, another type which appears like a cold abscess, and when incised an odorless sterile pus is obtained. In both types fragments of adult worms or microfilariae may be found.

In association with involvement of the spermatic cord or epididymis with or without signs of acute inflammation a hydrocele may occur. This is due to a filarial lymphangitis in these parts.

Chylous exudate into the pleura pericardium or peritoneum results from a blockage of the lymphatic duct pleural or pericardial or mesenteric lymphatics, which leads to a lymphedema of the serous membranes. Blockage of the renal or vesicle lymphatics produces chyluria and if hemorrhage also occurs it is called 'hematochyluria'.

The microfilariae are frequently found free in the blood stream or in any of the areas of lymphangitis adenitis or lymphoid tissue. During the acute



attacks there is a leucocytosis which may be as high as 40,000 per cu mm, and is chiefly composed of polymorphonuclear cells. After the exacerbation these decrease and an eosinophilia follows which may amount to from 20 to 30 per cent of the leucocytes.

**Pathological Anatomy**—The anatomical changes in filarial infection are due to the obstruction of the lymphatics by the adult worms. They may also obstruct the blood vessels and may invade the sinuses of the lymph



Fig. 496—Etiopiantia of the scrotum. The patient was a cannibal chieftain. (Courtesy of Dr. A. M. Hunter, U. S. Navy. From Sutton and Sutton, Diseases of the Skin.)



Fig. 497—Etiopiantia of the leg of a forty-year-old Negro. (Courtesy of Dr. W. H. Strotter. From Sutton and Sutton, Diseases of the Skin.)

phatic glands. When they die in these situations they usually lead to a permanent obstruction, although many of them are dissolved and are finally absorbed. Others however are surrounded by a capsule of fibrous tissue which may in time calcify and then can be recognized by the x ray.

**Diagnosis**—The recognition of this condition in endemic areas is not at all difficult and has only to be differentiated from acute septic lymphangitis or edema due to some local or general cause apart from filariasis.

**Prognosis**—The prognosis of filariasis as to life is good, provided the filaria have not invaded some vital tissue. The principal danger arises from secondary infections.

**Treatment—Prophylaxis**—The prevention of this infection is the same as that described in other diseases such as malaria transmitted by blood sucking insects. The *active* treatment of this disease has not been satisfactory although many drugs have been employed. In Puerto Rico they have advocated the use of antistreptococcus and antiplague serum, and antityphoid vaccine. These have seemed to prolong the interval between the attacks. If the position of the worms can be recognized by x ray much can be done through excision, but this is only effective when they are accessible. Amputation of elephantoid tissue of the scrotum has greatly relieved the local mechanical disability. Removal of lymphatic glands is not to be advised as traumatic elephantiasis may be added to the already existing condition.

### Dengue

**Synonyms**—Break bone fever dandy fever

**Definition**—Dengue is an acute specific infectious disease caused by an unknown filterable virus which is conveyed from man to man by the *Aedes aegypti* mosquito. It is characterized by exquisite pain in the limbs, a biphasic pyrexia and a rash toward the end of the febrile period.

**Etiology**—The filterable virus has not been discovered but it is apparently ultramicroscopic. The disease closely paralleled outbreaks of yellow fever (page 736) and the two diseases were often confused. They are both transmitted by the *Aedes* mosquitoes but by different varieties. In both there must be an interval of eight to twelve days between the infection of the vector and its capacity to transmit the disease to man.

**Symptoms and Signs**—The incubation period is from three to fourteen days and the portal of entry is the skin via the mosquito bite. There is a sudden onset with pyrexia and chilliness sometimes a rigor considerable malaise and intense pains in the muscles and bones. Headache and pain in the eyes are severe. There is diffuse flushing and injection of the skin conjunctivae mouth and pharynx. The pyrexia continues for a few days (two to four) when it returns to normal and all the symptoms rapidly improve. The pyrexia returns in several days and the symptoms return with greater severity. During the first phase, the pulse is rapid while in the second it is relatively slow. There is an early leucopenia with a relative lymphocytosis. Immature granulocytes are present and the mature ones are much degenerated. The spleen is not enlarged. With the second bout of fever a rash appears. This may be scarlatiniform or morbilliform, or intermediate. It fades with the fall of fever and leaves a fine desquamation. The urine may contain a trace of albumin and a few casts but never approaches the abnormal findings of yellow fever. Jaundice does not occur.

**Pathological Anatomy**—On account of the rarity of an opportunity for postmortem examination little is known of the anatomical changes produced by this infection. The few uncomplicated cases that have been examined

revealed general cloudy swelling of the viscera particularly of the liver which was also fatty and a few petechial hemorrhages chiefly in the gastrointestinal tract

**Diagnosis**—Dengue is to be differentiated from influenza rheumatic fever malaria and pappataci fever on account of the severe pains and the leucopenia. This seldom offers any difficulty. In the case of yellow fever the close similarity of many of the features which are common to both may and always have tended to confusion. The cause the vector the onset the flushing and the pyrexia with the remission make them closely allied. But the absence of jaundice hemorrhages and renal signs are against yellow fever while the pronounced leucopenia points to dengue.

**Course and Prognosis**—Recovery usually has occurred by the eighth to tenth day but convalescence is tedious the pains often persisting for weeks and there may be considerable mental depression and insomnia. The mortality is very low and occurs chiefly in the elderly or those suffering from chronic and debilitating illness.

**Treatment**—*Prophylaxis* is the same as that employed in yellow fever or malaria. The general treatment is symptomatic but morphia may be required to relieve the pains.

### Pappataci Fever

**Synonyms**—Phlebotomus fever sand fly fever

**Definition**—It is an acute specific infectious disease caused by a filterable virus transmitted by the sand fly (*Phlebotomus papatasi*) and characterized by pyrexia malaise and leucopenia.

**Etiology**—The filterable virus is carried by the sand fly a minute hairy insect which can pass through an ordinary screen or net. All sand flies are not vectors the particular one in this case being the *Phlebotomus papatasi*. As Leishmaniasis is also transmitted by a variety of sand fly it is better that this name should not be used. The female sucks blood and to transmit the disease she must bite a patient during the first two days of illness and six days thereafter she can infect others. The bites often produce local irritation.

**Symptoms and Signs**—The incubation is from four to ten days and the portal of entry is through the skin. The onset is sudden with pyrexia and a *chill headache and pain behind the eyes in the back of the neck* and legs are prominent. The face is flushed and the mucous membranes of the mouth and pharynx and conjunctivae are intensely injected. There is a pronounced neutropenia. There is no eruption. The fever lasts usually about three days although sometimes longer and rapidly returns to normal. The patient is usually much depressed during convalescence and there is a conspicuous bradycardia. Recovery always occurs and there is a short period of immunity then reinfection may occur.

**Diagnosis**—This disease may be confused with other febrile illnesses such as influenza malaria etc. but the true cause in this instance is soon found. It is more difficult to differentiate it from dengue in which there is also a leucopenia but the severity of pain and the eruption in the latter are distinctive.

**Treatment—Prophylaxis**—Protection from sand fly bites is the only method of prevention, as sand flies are almost impossible of extinction. Therefore fine netting (15 mm or less mesh) must be used in all ground floor windows and doors or as protection during sleep. The usual applications to the exposed parts to keep insects away may be used.

There is no specific treatment, which should therefore be symptomatic.

## LEISHMANIASIS

There are three diseases caused by different varieties of this protozoan parasite which belongs to the flagellata of the genus *Leishmania*. They are all conveyed to man, although perhaps not exclusively, by different sand flies. Two might be classified as local lesions, namely, oriental sore and espundia while the third kala azar, is a more systemic infection. The three varieties of *Leishmania* closely resemble each other. Each has two phases in its life history. On culture media and in the vectors they are flagellated, have a fusiform shape and with Giemsa stain blue with a relatively large red nucleus. In man they are aflagellate and are chiefly found within the endothelial and mononuclear cells where they multiply and eventually rupture the cell from which they escape to invade others. When they are taken into the intestine of certain insects the flagellate forms again appear. These multiply and eventually are infective to man.

### Oriental Sore

**Synonyms**—Cutaneous Leishmaniasis. Aleppo sore, frontier sore, tropical sore, Aleppo boil, Delhi boil.

**Distribution**—Oriental sore is found in the islands of the Mediterranean, Asia Minor, Northern Africa, Syria, the Arabian Peninsula, Mesopotamia, Persia, India, Turkistan and Nigeria.

**Etiology**—This infection is caused by the *Leishmania tropica*. It is transmitted by the sand fly, *Phlebotomus papatasi*, which is likewise the vector for pappataci or sand fly fever. It also occurs in dogs in endemic areas. It is prevalent in the natives of these areas in both sexes and all ages.

**Symptoms**—The incubation period is indefinite from a few days to months. The onset is characterized by single or multiple papules which gradually enlarge and are covered by scales. A serous exudate soon appears and the surface becomes moist and a small ulcer is produced. This has a sharp margin and slowly extends. The edges become raised and the surrounding tissue indurated. Secondary ulcers may form either through multiple original infections, or by direct seeding. The virus may also be transmitted from man to man. The primary nodule may disappear without ulcerating, or the local lesion may acquire a verrucose, lupoid or keloid character. There are few if any general symptoms. The duration of the primary lesion varies greatly. The ulcers may remain as granulating areas for periods of months or even more than a year and healing leaves a deeply pigmented retracted scar. Secondary infections modify the course considerably in that

they may make a local lesion much more severe and destructive, or give rise to symptoms of a generalized infection.

**Diagnosis**—The diagnosis is made by examining the discharge of the ulcerated area, or better that obtained by puncture of the surrounding induration. The parasites will be found in endothelial and large mononuclear cells and will readily stain by Giemsa. They may also be grown on N N N and other culture media at 22° C. The former consists of agar 14 grams, salt 6 grams, distilled water 900 c.c. and 1% as much defibrinated blood as agar is added at 52° C. and allowed to cool.

**Prognosis**—The prognosis from the local lesion is good as it is never fatal. Death occurs only from severe secondary pyogenic infections.



Fig. 498.—Photograph of a case of cutaneous Leishmaniasis—oriental sore (Cutest of Dr. J. L. Todd).

**Treatment**—*Prophylaxis* is accomplished by avoidance of being bitten by the sand fly, but this is almost impossible among the natives. When the primary sore occurs it should be treated as any ordinary infected area. The disease is promptly cured by antimony, which is given intravenously in a 2 per cent solution of sodium or potassium antimony tartrate or tartar emetic. The first dose is usually 2 c.c. and it is increased by 1 c.c. every other day until 5 c.c. are being injected. This is the maximum amount and should be continued until 4 grams of the drug have been administered. Other forms of antimony, such as Neostibosane and Ureastibamin (pentavalent compounds) have also been used with success (see page 1389). Other drugs have been advocated but it is best to use the specific antimony. Local treatment by x-ray has been brilliantly successful.

**Treatment — Prophylaxis** — Protection from sand fly bites is the only method of prevention, as sand flies are almost impossible of extinction. Therefore fine netting (1.5 mm or less mesh) must be used in all ground floor windows and doors or as protection during sleep. The usual applications to the exposed parts to keep insects away may be used.

There is no specific treatment, which should therefore be symptomatic.

## LEISHMANIASIS

There are three diseases caused by different varieties of this protozoan parasite which belongs to the flagellata of the genus *Leishmania*. They are all conveyed to man, although perhaps not exclusively, by different sand flies. Two might be classified as local lesions, namely, oriental sore and espundia, while the third kala azar, is a more systemic infection. The three varieties of *Leishmania* closely resemble each other. Each has two phases in its life history. On culture media and in the vectors they are flagellated, have a fusiform shape and with Giemsa stain blue with a relatively large red nucleus. In man they are aflagellate and are chiefly found within the endothelial and mononuclear cells, where they multiply and eventually rupture the cell from which they escape to invade others. When they are taken into the intestine of certain insects the flagellate forms again appear. These multiply and eventually are infective to man.

### Oriental Sore

**Synonyms** — Cutaneous Leishmaniasis, Aleppo sore, frontier sore, tropical sore, Aleppo boil, Delhi boil.

**Distribution** — Oriental sore is found in the islands of the Mediterranean, Asia Minor, Northern Africa, Syria, the Arabian Peninsula, Mesopotamia, Persia, India, Turkistan, and Nigeria.

**Etiology** — This infection is caused by the *Leishmania tropica*. It is transmitted by the sand fly *Phlebotomus papatasi*, which is likewise the vector for pappataci or sand fly fever. It also occurs in dogs in endemic areas. It is prevalent in the natives of these areas in both sexes and all ages.

**Symptoms** — The incubation period is indefinite, from a few days to months. The onset is characterized by single or multiple papules which gradually enlarge and are covered by scales. A serous exudate soon appears and the surface becomes moist and a small ulcer is produced. This has a sharp margin and slowly extends. The edges become raised and the surrounding tissue indurated. Secondary ulcers may form either through multiple original infections or by direct seeding. The virus may also be transmitted from man to man. The primary nodule may disappear without ulcerating or the local lesion may acquire a verrucose, lupoid or leloid character. There are few if any general symptoms. The duration of the primary lesion varies greatly. The ulcers may remain as granulating areas for periods of months or even more than a year and healing leaves a deeply pigmented retracted scar. Secondary infections modify the course considerably in that

lar over days or even weeks. When the disease is established the pyrexia assumes a double daily rise. The other symptoms are rapid anemia, leucopenia, thrombocytopenia, diarrhea, emaciation, edema, and great enlargement of the liver and spleen. There is an increase of plasma globins while a reduction in the plasma albumin fraction is on the contrary so great that the total plasma proteins are conspicuously reduced, which accounts for the edema (see page



Fig. 499.—*Leishmania donovani*. 1. In splenic mononuclear form, case of kala-azar.  $\times 1800$ . 2. Flagellated form from a culture.  $\times 1800$ . 3. Leishman-Donovan bodies in a smear made from a tropical ulcer.  $\times 1800$ . (Photomicrographs made at the U. S. Army Medical Museum.)

1256). The severity of the symptoms varies considerably from acute and fatal illness in a few weeks to a subacute and finally chronic type which may last for several years. In children and infants the irregular pyrexia with progressive anemia, lethargy, emaciation, purpura, and splenomegaly are the principal features.

In addition to the clinical picture outlined above many complications arise. These are probably due to a hemorrhagic tendency and secondary infec-

### Espundia

**Synonyms**—Mucocutaneous Leishmaniasis, American Leishmaniasis, Brazilian Leishmaniasis, nasopharyngeal Leishmaniasis, uta, and forest jaws

**Distribution**—Espundia is found in the countries of Central and South America, as far north as Mexico, and as far south as the Argentine

**Etiology**—This disease is caused by the *Leishmania braziliensis*. It is transmitted by the sand fly, *Phlebotomus lutzi*. It is claimed by some authorities to be identical with *Leishmania tropica*.

**Symptoms**—The incubation period is indefinite. The inoculation usually occurs on an exposed portion of the body and appears as a primary papule which soon ulcerates. It is indolent in healing, taking several months or years. Toward the latter part of this period, or after it has healed a nodular thickening of the mucous membrane of the nose develops. These nodules ulcerate and progressively invade the mucous membrane of the mouth, hard and soft palates, pharynx and larynx. There may be deep necrosis and destruction of the nasal cartilages. Untreated, the disease lasts for years and extensive destruction of tissue occurs in time.

**Diagnosis**—The diagnosis is comparatively easy by demonstrating the *Leishmania* in smears of the exudate or tissue puncture.

**Prognosis**—The prognosis for life is good as far as mortality from the immediate lesion is concerned, but secondary systemic infections leading to septicemia and pneumonia are the principal causes of death and before the specific treatment was discovered, the mortality from such secondary infections was very high.

The prophylaxis and treatment are the same as for oriental sore.

### Kala Azar

**Synonyms**—Infantile splenomegaly, nonmalarial remittent fever, black fever, visceral Leishmaniasis, infantile splenic anemia.

**Distribution**—This disease is endemic in the countries of the Mediterranean, southern Russia, India, Mesopotamia, China, Sumatra, and the head waters of the Blue Nile.

**Etiology**—Kala azar is caused by the *Leishmania donovani* and in contradistinction to the two previous forms of Leishmaniasis the parasites are found in the circulating blood either free or in the leucocytes. They are widely distributed in the endothelial cells of the internal organs, particularly where the reticuloendothelial system is abundant—spleen, liver, lymph glands, and bone marrow. In man they appear as small, oval or round bodies 2 to 5 microns in diameter, which contain the minute rodlike body called the blepharoplast. They are probably principally transmitted to man by the sand fly *Phlebotomus argentipes*, but experimentally it has been demonstrated that they can infect animals through ingestion of infected material and have been recovered from both the urine and the feces. Dogs are naturally susceptible.

**Symptoms**—The incubation period is indefinite and the onset is insidious with a progressive but irregular pyrexia. This irregularity occurs not only during a single day but may assume a quotidian type or be altogether irregu-



lar over days or even weeks. When the disease is established the pyrexia assumes a double daily rise. The other symptoms are rapid anemia, leucopenia, thrombocytopenia, diarrhea, emaciation, edema, and great enlargement of the liver and spleen. There is an increase of plasma globulin while a reduction in the plasma albumin fraction is on the contrary so great that the total plasma proteins are conspicuously reduced, which accounts for the edema (see page

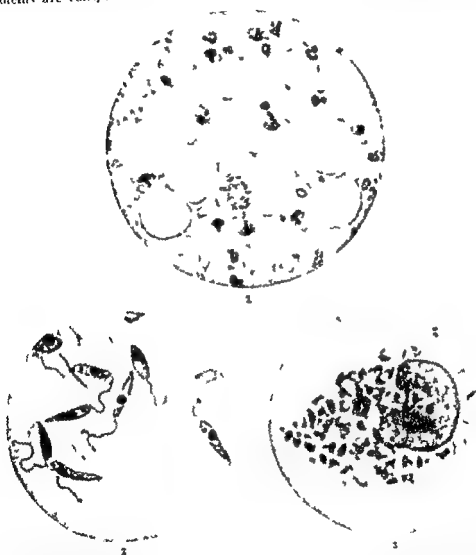


Fig. 499.—*Leishmania* sp. 1. In blood smear from kala-azar.  $\times 1500$ .  
2. Flagellated form from a culture.  $\times 1500$ .  
3. Tropical ulcer.  $\times 1500$ . (Photomicrographs made at U. S. Army Medical Museum.)

1256). The severity of the symptoms varies considerably from acute and fatal illness in a few weeks to a subacute and finally chronic type which may last for several years. In children and infants the irregular pyrexia with progressive anemia, lethargy, emaciation, purpura, and splenomegaly are the principal features.

In addition to the clinical picture outlined above many complications arise. These are probably due to a hemorrhagic tendency and secondary infection.

### Espundia

**Synonyms**—Mucocutaneous Leishmaniasis, American Leishmaniasis Brazilian Leishmaniasis, nasopharyngeal Leishmaniasis, uta, and forest jaws

**Distribution**—Espundia is found in the countries of Central and South America as far north as Mexico, and as far south as the Argentine

**Etiology**—This disease is caused by the *Leishmania braziliensis*. It is transmitted by the sand fly, *Phlebotomus lutzi*. It is claimed by some authorities to be identical with *Leishmania tropica*

**Symptoms**—The incubation period is indefinite. The inoculation usually occurs on an exposed portion of the body and appears as a primary papule which soon ulcerates. It is indolent in healing, taking several months or years. Toward the latter part of this period, or after it has healed, a nodular thickening of the mucous membrane of the nose develops. These nodules ulcerate and progressively invade the mucous membrane of the mouth, hard and soft palates, pharynx and larynx. There may be deep necrosis and destruction of the nasal cartilages. Untreated, the disease lasts for years and extensive destruction of tissue occurs in time.

**Diagnosis**—The diagnosis is comparatively easy by demonstrating the *Leishmania* in smears of the exudate or tissue puncture.

**Prognosis**—The prognosis for life is good as far as mortality from the immediate lesion is concerned, but secondary systemic infections leading to septicemia and pneumonia are the principal causes of death, and before the specific treatment was discovered the mortality from such secondary infections was very high.

The *prophylaxis* and *treatment* are the same as for oriental sore.

### Kala Azar

**Synonyms**—Infantile splenomegaly, nonmalarial remittent fever, black fever visceral Leishmaniasis infantile splenic anemia

**Distribution**—This disease is endemic in the countries of the Mediterranean, southern Russia, India, Mesopotamia, China, Sumatra and the head waters of the Blue Nile.

**Etiology**—Kala azar is caused by the *Leishmania donovani* and in contradistinction to the two previous forms of Leishmaniasis the parasites are found in the circulating blood either free or in the leucocytes. They are widely distributed in the endothelial cells of the internal organs particularly where the reticuloendothelial system is abundant—spleen, liver, lymph glands and bone marrow. In man they appear as small oval or round bodies 2 to 5 microns in diameter, which contain the minute rodlike body called the blepharoplast. They are probably principally transmitted to man by the sand fly *Phlebotomus argentipes*, but experimentally it has been demonstrated that they can infect animals through ingestion of infected material and have been recovered from both the urine and the feces. Dogs are naturally susceptible.

**Symptoms**—The incubation period is indefinite and the onset is insidious with a progressive but irregular pyrexia. This irregularity occurs not only during a single day but may assume a quotidian type or be altogether irregu-

■ important, as a diffuse bronchitis leading to pneumonia sometimes complicates this treatment. There may also be a papular eruption suggestive of the Brachmachari dermal Leishmaniasis mentioned above. Kala azar does not respond to specific treatment as promptly as does espundia and oriental sore. Several weeks usually elapse before the temperature returns to normal and more than one course may be required but the general condition of the patient rapidly improves. In infants and children proportionate doses are employed ranging from 0.5 cc of a 2 per cent solution for infants (2 cc maximum dose) to 1 cc for a child of ten to twelve years (3 cc maximum dose). Ureastibamin and neostibosane (pentavalent antimony compounds) are more efficacious. The usual dosage of the former is 0.1 to 0.2 gm intravenously every second third or fourth day until 1 to 4 gm in all are given. Neostibosane may be given either intramuscularly or intravenously in dosage of 0.1 to 0.3 gm every other day or daily until 1 to 5 gm have been given. The dosage and duration are varied according to the age and severity of the cases. A vigilant follow up should be carried out with liver or spleen puncture if necessary to forestall recurrences and effect a cure.

### Trypanosomiasis

Trypanosomiasis may be of two clinical varieties. They are caused by flagellate protozoa genera *Trypanosoma* and *Schizotrypanum*. Two types of trypanosomes are found in Africa namely, *Trypanosoma gambiense* and *Trypanosoma rhodesiense* which are indistinguishable as are the clinical features except that the former tends to be more chronic than the latter. They are both transmitted to man by *Glossina* (tsetse fly) chiefly the palpalis and morsitans. There is also a South American variety which is due to the *Schizotrypanum cruzi*. This is transmitted to man by a biting insect usually one of the *Triatoma* the commonest being the *mcLinsti*. It is claimed by some to be inoculated from the crushed insect into scratches, bite punctures or other abrasions while others claim it may be directly introduced into the blood stream at the time of the bite.

### African Sleeping Sickness

#### Synonyms—African trypanosomiasis

**Distribution**—The distribution of the infection due to the *Trypanosoma gambiense* is from Senegal to Angola on the west coast of Africa in the central portion contiguous to the lakes Victoria Albert and Bangwelo the Belgian and Portuguese Congo French Equatorial Africa and in addition Western Mongolia and the islands of the Gulf of Guinea. The *Trypanosoma rhodesiense* infests northeastern Rhodesia Nyasaland Portuguese East Africa and southern Kenya.

**Etiology**—As these two trypanosomes are indistinguishable one description will serve for both. They are found in the blood and the spinal fluid and stain readily with Giemsa. They have a spindle shaped body, miss the cytoplasm of which stains blue with a large oval red staining nucleus or trophic nucleus. This is situated at one end of the cell and also contains a red dot

tions. Noma or cancrum oris (see Chapter II) is particularly common in children and is probably due to the pronounced neutropenia. There may also be bleeding from the gums, purpura, cerebral hemorrhage, melena, and hematemesis while among the infections there may be bacillary or amebic dysentery, septicemia, bronchitis, pneumonia, otitis media, mastoid disease, etc. A late complication or sequela is the development of cutaneous nodules in the skin which were first described by Brachmachari. These are usually preceded by a leucoderma and follow the administration of antimony. On biopsy, *Leishmania donovani* can be demonstrated and also grown from these tissues. It has been suggested that this is a dermatological form, as the parasites cannot be demonstrated in the peripheral blood or in the spleen. These cutaneous lesions often occur in groups.

**Diagnosis**—The direct diagnosis of kala azar depends upon the demonstration of the parasite either in the peripheral blood or in spleen, liver, or gland pulp obtained by puncture. From such material they may also be grown on artificial media. There are several tests which are an aid but are not absolutely diagnostic. The first is the formal gel test advocated by Napier and Muir. To 1 cc of the patient's serum a drop of 30 per cent formalin is added. In two to three minutes the serum is completely jellyed, and within twenty minutes is coagulated to a consistency of boiled egg white. If the cases are under three months' duration there is first a cloudiness but the serum does not jelly and in 24 hours is yellowish white. The second test is the Brachmachari reaction which consists of adding one part of the patient's serum to 2 parts of distilled water; a cloudiness and a precipitate appear. The third test is the Chopra antimony reaction. The patient's serum is diluted ten times with a saline solution and to this is added an equal part of 4 per cent antimony solution (ureastibium preferred). A pronounced cloudiness appears.

Kala azar is to be differentiated from malaria, tuberculosis, relapsing fever, undulant fever and typhoid and paratyphoid fevers. A careful analysis of the clinical picture and the employment of specific tests for these diseases seldom fail to indicate a proper conclusion.

**Prognosis**—The death rate from kala azar in untreated cases varies from 75 to 95 per cent. Particularly is the mortality high in the acute variety or when cancrum oris, secondary infections or hemorrhages develop. Specific treatment has reduced the mortality to between 5 and 15 per cent but there are some cases which are resistant and these practically all die. There is little doubt that mild cases recover although not recognized.

**Treatment**—The prophylaxis depends upon the segregation of the infected individual thereby preventing the vector (sand fly) from transmitting the disease, and finally the prevention or avoidance of being bitten by these insects as no means of exterminating them has as yet been discovered.

The active treatment rests upon the use of the specific remedy, antimony either in the form of tartar emetic or preferably sodium or potassium antimony tartrate used in the same manner as that outlined for espundia. In kala azar there is usually an exacerbation of the pyrexia after each treatment which may be accompanied by headache, vomiting and cough. The last symptom

looked for in the blood cerebrospinal fluid gland puncture juice and if not detected in smears animal inoculation should be carried out. The disease in its early stages is to be differentiated from malaria typhoid fever and relapsing fevers.

**Prognosis**—If the infection is recognized in the early stages and proper treatment is instituted the outlook is good. If not even with treatment the eventual result is always in doubt and in untreated cases the mortality is practically 100 per cent.

**Treatment**—The active treatment consists in the early use of arsenicals particularly atoxyl tryparsamide and Bayer 203 (germanin). Antimony preparations such as the trioxide tartar emetic or the double salt of antimony tartrate have also been employed. In the more chronic stages tryparsamide is the drug of choice. It should be given in 0.5 to 3 gram doses but never in amounts greater than 0.035 grams per kilo of body weight. Four injections on alternate days are given and then a month's interval is allowed to elapse before a second series is administered. It may be necessary to continue up to 15 or 20 courses. Larger individual doses are apt to produce various toxic symptoms such as amblyopia optic atrophy jaundice etc. such as have been noted in the treatment of syphilis by arsenic.

### Chagas Disease

**Synonyms**—Brazilian trypanosomiasis or schizotrypanosomiasis

**Distribution**—This infection is found in Peru, Brazil, Panama and Venezuela.

**Etiology**—It is due to the *schizotrypanosoma cruzi*. This parasite is found in the circulating blood as a typical trypanosome but in the cells has a form resembling a *Leishmania*. It multiplies only in the cell and consequently destroys it. The trypanosomes free in the blood stream are about 30 microns in length and contain a large blepharoplast a nucleus and have an undulating membrane and a free flagellum. In the cells however in the form of *Leishmania* they measure 2 to 5 microns and have only a nucleus and blepharoplast.

**Symptoms**—There is an acute and a chronic form. The former is most commonly found in children with *parexia* and after about 3 weeks there is a tissue pseudoedema caused by a deposit of mucoid material. This does not pit on pressure but gives to the face and eyelids a swollen edematous appearance which closely resembles myxedema. Of the viscera there is enlargement of the lymph glands liver spleen and thyroid and acute leucitis is quite characteristic. The acute stage lasts from 2 to 4 weeks and if untreated the patient usually dies or lapses into the chronic state. The latter is most common in adults. The symptomatology depends upon localization of the trypanosomes and therefore mixedematous nervous cardiac thyroid suprarenal ovarian and other types have been described depending upon the principal situation of the organismal involvement.

**Pathological Anatomy**—The anatomical changes result from the *Leishmania* destroying the invaded cells. They are most frequently found in those tissues described above which have given names to different subvarieties but they may be also found in any tissue.

or blepharoplast to which is attached a single flagellum which tapers out from an enveloping membrane but is free at the anterior extremity. They measure from 15 to 30 microns in length, and 15 to 25 microns in width. They increase through binary longitudinal division. In the fresh blood smears they are actively motile.

**Symptoms**—The incubation period is from 10 to 14 days for the *Trypanosoma rhodesiense*, and that of the *Trypanosoma gambiense* 2 to 4 weeks. The onset is rather insidious with irregular pyrexia, lymphadenopathy, splenomegaly, asthenia and a fleeting erythematous rash. Localized or widespread edema soon appears. In the more chronic stages symptoms referable to the central nervous system are conspicuous. There is intense headache, mental lethargy, physical asthenia, and progressive somnolence. There may be retraction of the head, opisthotonos, local paralysis, convulsions, incontinence of urine and feces, coma, with succeeding death. In the advanced stages there is pronounced anemia. Iritis, cystitis and chorioretinitis are common in the chronic cases. The infection by the *Trypanosoma rhodesiense* is much more acute and severe than that of the *Trypanosoma gambiense*; it may last for several weeks. Occasionally mild cases are found.



Fig. 500—Trypanosoma is *Trypanosoma gambiense*. The sleeping sickness trypanosome.  $\times 1400$  (Photomicrograph made at the U. S. Army Medical Museum.)

**Pathological Anatomy**—The principal anatomical changes are found in the lymph glands which are enlarged, particularly the submaxillary, bronchial, mesenteric, inguinal and femoral. There is hyperplasia of the lymphoid tissue and trypanosomes may be found here as well as in the connective tissue of any organ and particularly in the central nervous system where the spinal fluid is found increased in amount, turbid from increased cells, the number of which give a rough index of the degree of cerebrospinal involvement. The fluid often contains trypanosomes. In protracted cases a chronic leptomenigitis occurs.

**Diagnosis**—There are few diseases in which an early diagnosis is so important as in trypanosomiasis, as the eventual success of the treatment is greatly influenced thereby. In all suspected cases the parasite should be

be a comparatively rare disease, but this is quite wrong, for although it does not occur in epidemic proportions, it is endemic in many countries of which North America is not an exception, and unless prophylactic vaccination is maintained in a high percentage of the population epidemics are to be expected in the future.

**Etiology**—Up to recent years the cause of smallpox was unknown, but now there is sufficient evidence to warrant the statement that it is due to a filterable virus. This can be transmitted by the washings of the nose and nasopharynx, the fluid of the vesicles, and the dried exudate of the scabs, but so far it has not been transmitted by blood or serum. Inclusion bodies in the cytoplasm of the epithelium of the skin were first described in 1892 by Guarnieri, and it is still debatable whether these represent the virus itself or the result of cellular reaction to the virus. There are also found intranuclear bodies, and the exact role of these in the etiology is still in doubt.

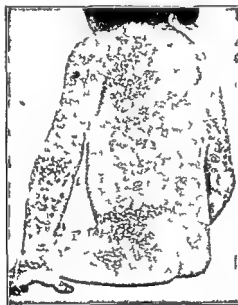


Fig. 501.—Varicella. (Courtesy of Dr. Jay E. Schamberg. From Sutton and Sutton, Diseases of the Skin.)

**Symptoms**—The incubation period is between ten and twelve days. Although longer and shorter periods have been recorded, it is doubtful whether these are accurate. The onset is sudden, with chills and severe pyrexia characteristic of many acute infections, but in this disease are significant in their intensity. There are exquisite headache, severe pains in the extremities and in the lumbar region. The last is more severe in smallpox than in any other infectious disease and is therefore considered to have some diagnostic significance. The pyrexia soon mounts to 103° or 104° F. and continues with little remission for two or three days. During this time there may be scarlatiniform or morbilliform rashes which may be diffuse but more usually are confined to the area between the umbilicus and the mid thighs. Petechiae may also occur either in this area or elsewhere. At the end of this period the temperature usually re-

**Diagnosis**—This can be arrived at only by finding the parasite in the blood or the spinal fluid. It is most frequently present in the former during the febrile attacks. The diagnosis cannot be made with any accuracy on the clinical symptoms alone.

**Prognosis**—The prognosis in well established cases is always grave in adults. Children occasionally recover from the acute stage, but in chronic cases it is almost hopeless.

**Treatment**—*Prophylaxis*—This is similar to all diseases transmitted by biting or blood sucking insects. The isolation of the infected population is of greater importance if that be possible. Unfortunately there is no specific treatment for this disease although the drugs outlined in the treatment of African sleeping sickness may be employed but the results have been most discouraging.

### INFECTIONS WITH AN UNCERTAIN PORTAL OF ENTRY

All infectious diseases so far described have had a fairly definite portal of entry, and in many of them the causative agent has been known or surmised. There remains now to describe a number of infections the portal of entry of which would seem most probably to be through the nasal mucous membrane. These are smallpox or variola, varicella, or chickenpox, herpes zoster, infectious mononucleosis, epidemic pleurodynia, swineherd's disease and leprosy. It is interesting to note that among the Chinese a favorite site for the inoculation of the virus of smallpox or cowpox, to induce a protective immunity, is through the nasal mucous membrane. In regard to leprosy there is little to indicate where the bacilli gain entrance but it has been suggested that the most likely portal is through the mucous membrane of the nose or nasopharynx.

#### Smallpox

**Synonym**—Variola

**Definition**—Smallpox is an acute infectious disease caused by a specific filtrable virus. It has an acute onset with headache, pain in the back and soon develops a characteristic vesicular eruption.

**Epidemiology**—Smallpox is one of the most infectious of diseases and is transmitted in the early stages by air borne droplets of nasal secretion, and in the later stages by the dried particles from the scabs of the eruption. The virus can be transmitted directly from man to man or by household utensils or clothing, and epidemics have been recorded as beginning from bodies of smallpox victims recently buried and disinterred.

Up to recent times periodic epidemics of this disease have occurred, some times covering large areas. The virulence varied considerably not only in different epidemics but in different periods of an epidemic. Before protective vaccination was more uniformly introduced the incidence was highest in children, as adults had practically all been exposed and had probably contracted a mild unrecognized infection or had obviously had the disease. It was most disastrous in communities or races in which the disease had not been present for some decades or which had never been exposed. It is supposed now to



hard but within a few days develop an umbilicated vesicle surrounded by a small red areola. These are multilocular as they do not collapse with a single needle prick. After another two or three days the vesicles become pustular, and the umbilication disappears. They gradually shrivel and about the twelfth day have dried up, producing scabs which soon desquamate. If the pustular eruption has been confluent, large areas of skin may be shed in one cast. The depth of the pustular ulceration is usually sufficient to leave definite pitting and scarring. This is aggravated by scratching which is difficult to prevent because of their intense itchiness.

The variable character of the eruption has given rise to a number of clinical forms of this disease. If it does not become purulent it is called 'abortive' while if the eruption is scanty and leaves little or no pitting, it is called "varioid." When there are hemorrhages into the skin and mucous membranes it is called "black" or 'hemorrhagic' smallpox. The appearance of petechiae in the early stages indicates the probability of this type developing later which is probably due to an intense toxemia affecting the permeability of the capillaries as in some forms of purpura, and in such hemorrhages from the mucous membranes of the mouth, stomach and bowel are not uncommon.



Fig. 61.—A single pustule which developed following vaccination. The patient, a man aged twenty-three, had never before been vaccinated (Courtesy of Dr. E. L. Stewart. From Sutton and Sutton. Diseases of the Skin.)

With the pustular stage of the eruption the pyrexia returns and its severity is in proportion to the extent of the suppuration and continues until desiccation begins when it may fall either by lysis or crisis. This secondary fever is attributed in most part to the pyogenic infection of the skin. In direct proportion to the extent of the eruptive lesion there may be intense toxemia, delirium and edema of the skin particularly of the face and eyelids. When the mucous membranes of the mouth, pharynx and larynx are involved there is considerable pain in these parts and a change in the voice may be noted. There is usually a general adenopathy particularly in the cervical region and the liver and spleen are palpable.

The urine is highly colored, reduced in amount as in all infections unless large amounts of fluids are taken. There is a leucocytosis which is in proportion to the pustular eruption and may rise to 30,000 or 40,000 per cu mm. It is principally due to an increase of the polymorphonuclear cells. In the severe toxic cases particularly those with hemorrhage a relative neutropenia may be found probably due to a toxic effect upon the bone marrow. In all cases there is a thrombocytopenia but this is only pronounced in the purpuric cases and may have some role in the causation of hemorrhages.

The visceral organs are seldom involved in smallpox. The renal changes as already noted are merely those of a general infection. Such secondary

turns to normal with a great improvement in the patient's general condition, and at the same time the preliminary eruption appears over the wrists, fore head and face. The hands and feet, particularly the palms and soles, seldom escape: This consists of reddish macules up to 3 mm in diameter



Fig 50 —Discrete smallpox in an unvaccinated female (Courtesy of Dr Samuel Sweitzer From Sutton and Sutton Diseases of the Skin)



Fig 502—Variola of the confluent type (Courtesy of Dr Watson Campbell and Dr C. S. Newman From Sutton and Sutton Diseases of the Skin)

which pale somewhat on pressure. The eruption soon becomes papular and rapidly spreads over the trunk and limbs and may appear on the mucous membrane of the mouth, nasopharynx, and nose. These papules are quite

hard but within a few days develop an umbilicated vesicle surrounded by a small red areola. These are multilocular as they do not collapse with a single needle prick. After another two or three days the vesicles become pustular, and the umbilication disappears. They gradually shrivel and about the twelfth day have dried up producing scabs which soon desquamate. If the pustular eruption has been confluent, large areas of skin may be shed in one cast. The depth of the pustular ulceration is usually sufficient to leave definite pitting and scarring. This is aggravated by scratching, which is difficult to prevent because of their intense itchiness.

The variable character of the eruption has given rise to a number of clinical forms of this disease. If it does not become purulent, it is called "abortive", while if the eruption is scanty and leaves little or no pitting it is called "varioloid". When there are hemorrhages into the skin and mucous membranes it is called 'black' or hemorrhagic smallpox. The appearance of petechiae in the early stages indicates the probability of this type developing later which is probably due to an intense toxemia affecting the permeability of the capillaries as in some forms of purpura and in such hemorrhages from the mucous membranes of the mouth stomach and bowel are not uncommon.



Fig. 504.—A single pustule which developed after vaccination. The patient, a man aged twenty, had never before been vaccinated. (Courtesy of Dr. L. L. Stearns, from Sutton and Sutton. "Diseases of the Skin.")

With the pustular stage of the eruption the pyrexia returns and its severity is in proportion to the extent of the suppuration and continues until desiccation begins when it may fall either by lysis or crisis. This secondary fever is attributed in most part to the pyogenic infection of the skin. In direct proportion to the extent of the eruptive lesion there may be intense toxemia, delirium and edema of the skin particularly of the face and eyelids. When the mucous membranes of the mouth, pharynx and larynx are involved there is considerable pain in these parts and a change in the voice may be noted. There is usually a general adenopathy particularly in the cervical region and the liver and spleen are palpable.

The urine is highly colored, reduced in amount as in all infections unless large amounts of fluids are taken. There is a leucocytosis which is in proportion to the pustular eruption and may rise to 30 000 or 40 000 per cu mm. It is principally due to an increase of the polymorphonuclear cells. In the severe toxic cases particularly those with hemorrhage a relative neutropenia may be found probably due to a toxic effect upon the bone marrow. In all cases there is a thrombocytopenia but this is only pronounced in the purpuric cases and may have some role in the causation of hemorrhages.

The visceral organs are seldom involved in smallpox. The renal changes as already noted are merely those of a general infection. Such secondary

lesions as do occur can all be accounted for by a bacterial septicemia and include bronchitis, bronchopneumonia, arthritis, osteomyelitis, otitis media, keratitis, and furunculosis. Quite separate from these secondary pyogenic infections are a group of lesions analogous to the involvement of the nervous system in other virus diseases, such as poliomyelitis, herpes zoster, encephalitis, and include peripheral neuritis, myelitis, hemiplegia, and other focal cerebrospinal lesions.

Smallpox is one of the few diseases which has been demonstrated to affect the fetus *in utero*.

**Pathological Anatomy**—The principal tissues involved in smallpox apart from the skin are the blood vessels and the reticuloendothelial system. In the skin there is a degeneration of the cells of the lower layers of the epidermis in which the inclusion bodies can be found, and in the exudate of the eruption the virus is contained in great concentration. There is also conspicuous proliferation of the reticuloendothelial tissues, and it has been suggested that this has a relation to the hemorrhagic tendency. Also the widespread involvement of the bone marrow is a prominent feature in this disease. The liver and spleen are enlarged, particularly in children.

**Diagnosis**—It is most important that a correct diagnosis of smallpox should be arrived at before the eruption has appeared. During an epidemic this is comparatively easy. It is in sporadic cases, however, that there is great danger of their being the cause of a severe epidemic. It must be differentiated from influenza, measles, dengue and epidemic meningococcal meningitis. There may be considerable pharyngitis and with the preliminary rash may lead to confusion with scarlet fever or measles or with erythematous rashes which so frequently accompany a streptococcal sore throat. The principal features in favor of smallpox are the fact that the patient has not been vaccinated, the intensity of the onset, the constant occurrence of exquisite headache and pain in the back, but these symptoms are not particularly distinctive. Therefore in isolated cases it is usual for the proper diagnosis to await the eruption. At this stage the principal disease from which smallpox should be differentiated is chickenpox or varicella and particularly is this important in the mild cases of the former. The onset of chickenpox is less explosive, constitutional symptoms are mild, the eruption appears on the first day and in distinction to smallpox it develops in successive crops. Therefore macules, papules, vesicles and pustules may be present at the same time. In smallpox the eruption follows a regular sequence and is practically the same in its entire distribution at the different stages. In chickenpox the vesicles are unilocular and are not umbilicated. The papules are soft as compared to the hard, short, primary eruption of smallpox. Further the eruption in chickenpox lasts about three days. If there is any doubt the patient should be rigidly isolated. Other bullous eruptions that may be confused with smallpox are bullous syphilides, impetigo contagiosum, pemphigoid lesions and drug rashes.

**Prognosis**—This depends to a great extent upon the character of the epidemic and whether or not the patient has been vaccinated, and how many

years previously. In the unvaccinated the mortality has varied from 30 to 60 per cent, while in the vaccinated, although they may contract the disease it is usually of the abortive or varioloid form. An early purpuric eruption is of serious significance as is also a confluent eruption which leads to extensive destruction of the skin surfaces and massive absorption of septic material. A scant or discreet eruption indicates a good result.

**Treatment—Prophylaxis—**The best prophylaxis is compulsory vaccination of children during their first year and this should be repeated every five to ten years. The great danger of an epidemic arises from a mistaken diagnosis of a case in an unvaccinated community. Once the disease has been recognized, the patient or patients should be strictly isolated and the health authorities in all contiguous communities should be notified. The attendants upon these cases should also be isolated in the same building with the patients and should not be allowed to intermingle at any time with the rest of the population.

**Vaccination—**From ancient times there are records of attempts to produce mild infections of smallpox through artificial inoculation under selected conditions. It has already been noted how the Chinese introduced infected material into the nose. In India the infective material was applied to the skin and the Persians ingested the crusts. It was in eastern Europe (Turkey) that the infected material was first introduced into the skin by scarification. Although these methods were at times quite successful the risk was great but perhaps not greater than the risk of ordinary contagion. In the eighteenth century it became common knowledge among farmers that individuals who had contracted cowpox did not contract smallpox and this became a domestic manner in which smallpox could be prevented. Jenner, hearing of this undertook the inoculation of the cowpox infected material into humans and published his first results in 1798. There now seems little doubt that the virus of cowpox and that of smallpox are identical. For many years the virus was transferred from man to man. The first refinement was the collection of the vesicular fluid which was dried on small sharp instruments usually made of ivory which were called vaccine points. With the discovery of the role of bacteria in infection aseptic methods were introduced and now the fluid for vaccination is prepared under the most rigid aseptic precautions from infected calves. The virus for vaccination is also cultivated on the allantoic membrane of the chick. The favorite site for the inoculation is the upper and outer aspect of the left arm but for cosmetic reasons this has been changed to the outer and upper aspect of the thigh in the female. At the selected spot for vaccination the skin is sterilized and under aseptic conditions the superficial layers of the skin are scratched with a needle. It is inadvisable to produce deep excoriations but just sufficient for serum to appear. A drop of vaccine is placed on this area and allowed to dry. Dressings or protective shields are not advisable as they restrain the individual from local cleanliness and are more likely to promote infection than to prevent it. About the fourth day one or more small papules develop. Vesicles appear on the next day and at this time there may be slight pyrexia and the spleen may be felt. Surrounding the vesicle there is an erythema and secondary vesicles may

develop. The pyrexia continues to increase for two to three days, and by the eighth day reaches its maximum, when there is also a local adenopathy. The local area has now become quite swollen and edematous and it is best to keep the arm in a sling, and the patient confined to bed. By the eleventh or twelfth day the local lesion begins to recede, and the reaction rapidly fades to a dry, brown crust which separates from the skin at the end of the third week, leaving a depressed scar. In other words a mild infection has been produced. Rarely a diffuse eruption occurs. This description applies to the more violent of reactions, many of them are extremely mild without any systemic disturbance or excessive local reaction. It is best to vaccinate all children within the first year, and to revaccinate them before the end of the tenth although in revaccinated individuals a reaction or "take" may not occur. The milder the reaction the more rapidly does it develop and recede, indicative of an already existing partial immunity. If no reaction occurs and the vaccination has been well done, it may be presumed that the patient is completely immune. As the incubation period of smallpox is twelve to fourteen days, vaccination immediately after exposure is indicated.

Vaccination has been criticized and the procedure attacked on account of the occasional sequelae. Pyogenic infections may be severe and are of course due to faulty technique or lack of personal cleanliness. Tetanus has also been reported and is due to the same causes. Of a different order are the very occasional cases of encephalitis. It usually appears on the tenth day after vaccination and would appear to be closely related to, if not identical with the encephalitic lesions associated with smallpox.

The active treatment of smallpox is similar to that of any other acute infection. The headache and pain in the back and limbs may be relieved by analgesics such as aspirin, phenacetine, and even morphine. During the stage of eruption great care must be taken of the eyes, mouth, throat and skin. The former must be frequently irrigated with a mild antiseptic solution and oily sprays should be used in the nose and nasopharynx. The care of the skin is more difficult. Many measures have been advocated but most have been found to have little value. The local irritations should be relieved by all means in our power but in confluent cases this is extremely difficult. Scratching should be prevented by bandaging the hands. Perhaps the most hopeful method of treatment is continuous warm saline baths but even here this can only be used to a limited extent. When desiccation and desquamation commence the general application of vaseline containing 2 to 3 per cent phenol often relieves the intense irritation. The general toxemia is combated by the usual methods employed in any severe infectious disease. The diet should be nutritious with small residue and copious amounts of water should be given.

As much of the toxemia and mortality is due to the secondary infection of the skin with the *Staphylococcus aureus* and other pyogenic bacteria sulfonamides and penicillin have been a great boon. These should be given in full doses during the period of the eruption in the first instance as a prophylactic to the intensity of the pyogenic invasion and second to control it during the purulent stage of the eruption (see Chapter XX).

### Chickenpox

**Synonyms**—*Varicella*, 'Glasspox.'

**Definition**—This is an acute specific disease which is extremely contagious and the principal sign of infection is a vesicular eruption.

**Etiology**—The exact cause of chickenpox is unknown. It is most likely due to a filterable virus and there has been considerable discussion as to its relation to herpes zoster, it being claimed by some that an attack of varicella protects from herpes zoster and vice versa. As yet this is not proved. There is some clinical evidence to suggest varicella may be contracted from persons with herpes zoster. Infants are most susceptible to it. It is transmitted by the droplets from the nasopharynx and by the dry crusts from the eruption. It may be carried by clothing, by the hands or may be air borne.



Fig. 50.—Varicella in an adult. (Courtesy of Dr. E. Wood Ruggles. From Sutton and Sutton: Diseases of the Skin.)

**Symptoms**—The incubation period is about fourteen days, and the onset is acute. The eruption appears on the first day. As in smallpox, a scarlatiniform or morbilliform prodromal eruption may occur. The systemic symptoms are usually negligible. There may be slight pyrexia and some malaise. The eruption appears first as a small macule and is distinct from that of smallpox in being soft and does not have the deep-seated hard papular character of the more grave disease. A vesicle rapidly appears which is round or oval surrounded by a small areola and is unicellular. Umbilication is not conspicuous. It is easily ruptured and seldom leaves a scar as in smallpox. The eruption develops in successive crops which are most numerous on those parts of the skin subject to irritation although it first appears on the face and spreads rapidly over the trunk and extremities. All stages—macules, vesicles and pustules—may be present at the same time.

**Complications**—Complications of chickenpox itself are rare except secondary pyogenic infections, such as furunculosis, cellulitis, impetigo and erysipelas. Like other virus diseases, encephalitis and poliomyelitis sometimes occur. Severe involvement of the mucous membranes is uncommon, but occasionally a distressing pharyngitis or laryngitis—the latter may require intubation—may meet with. Relapses seldom occur and second attacks are practically unknown.

**Pathological Anatomy**—There are no characteristic anatomical changes in this disease.

**Diagnosis**—As in smallpox, varicella is to be differentiated from other vesicular or bullous lesions, but this is comparatively easy except so far as smallpox itself is concerned. A severe attack of chickenpox may closely simulate a mild attack of smallpox. The description of the two eruptions would seem so distinct as hardly to suggest such confusion, but in practice this is another matter and epidemics of smallpox have been traced to such mistakes.

**Prognosis**—The mortality from this disease is very low, and when death occurs, it can usually be attributed to secondary infections or to some other disease.

**Treatment**—*Prophylaxis*—Isolation of all cases of chickenpox should be continued until the crusts have all disappeared and the individual has been subjected to a series of antiseptic baths. All clothing, bedding and utensils as well as the sickroom itself should be thoroughly disinfected. In institutions convalescent serum has been used to convey a passive immunity with some success.

The active treatment of the patient is that of any other acute infection. The most important objective is preventing the child from scratching the irritating eruption as this not only aggravates the local condition but may produce secondary infections which lead to scar formation which otherwise does not occur. If the eruption is not too extensive each individual lesion may be painted with equal amounts of tincture of iodine and alcohol. Warm baths twice a day give great relief and are also helpful in preventing secondary infections. As in smallpox the sulfonamides and penicillin are indicated to control the pyogenic infection of the eruption.

### Herpes Zoster

**Synonyms**—Shingles, zoster, zona.

**Definition**—Herpes zoster is an acute infectious disease which is probably due to a filtrable virus which affects the spinal posterior root and the extramedullary cranial nerve ganglia. It is characterized by a painful vesicular eruption of the skin and mucous membranes.

**Etiology**—Although a virus has not been identified this probability is supported by the presence of intranuclear inclusions in the cells of the skin lesions and the reported experimental transmission in man. The portal of entry and the way the virus reaches the ganglia are not known. Furthermore the occurrence of symptomatic herpes is in mumps, lobular pneumonia, meningococcal meningitis, etc., and its presence in association with lesions about the ganglia have never been explained.



**Symptoms and Signs**—The onset is usually rather sudden with pain in the region of the sensory nerve distribution malaise and fever. In three to four days an erythematous and vesicular eruption appears in these areas. Lumbar puncture usually reveals an increased cell count. In a few days the general symptoms disappear the vesicles dry up and soon heal unless delayed by secondary infection.

Any one or more of the spinal ganglia may be and are most commonly involved. Although any of the cranial nerves may be affected it is rare except for the first branch of the sensory division of the trigeminal nerve. This may lead to corneal ulceration which is serious and requires expert ophthalmologic attention.

**Prognosis**—This is always good and complete recovery is the rule. Pain over the area of eruption may persist for many weeks and even months particularly in elderly people. It may be most troublesome and very refractory. There is rarely a residual paralysis.

**Diagnosis**—This is divisible into the preeruptive and posteruptive phases. In the former pain is the outstanding feature and may be confused with pericarditis coronary occlusion pleurisy cholecystitis appendicitis or other acute visceral lesion. When the eruption appears the diagnosis is quite clear. There are however cases in children and occasionally in adults where numerous vesicles unrelated to the nerve distribution appear and closely simulate varicella. In fact as mentioned on page 1599 there is clinical and epidemiological evidence which would indicate that the viruses of these two diseases are closely related.

**Treatment**—There is no specific cure for this disease. Therefore as would be expected all and sundry remedies have been advocated on scant evidence and with no consistent success. The prolonged pain may be so disturbing as to require posterior root section or ganglionectomy.

### Lymphocytic Choriomeningitis

**Definition**—This is an acute infectious disease with mild influenza like prodromata followed in some instances by acute lymphocytic meningitis. It is due to a filtrable virus and has a wide distribution in North America Europe and Asia.

**Etiology**—The virus is of medium size and affects many laboratory animals as well as man. The method of transmission is not known but certain blood sucking insects have been shown to transmit the virus experimentally. Therefore there may be several avenues of infection.

**Symptoms and Signs**—The incubation period is a few days. The first period is characterized by general malaise pains in limbs headache slight prostration and moderate fever with a leucopenia. There may also be a sore throat and cough. This phase lasts for a few days to several weeks with gradual improvement and the fever disappears. After a lapse of one or two days it returns with the signs of meningeal irritation—headache drowsiness nausea vomiting stiffness of the neck and Kernig's sign. The leucopenia has now disappeared. The spinal fluid shows increased pressure and a lymphocytosis of 100 to 1000 or more per cumm. with increased protein and nor-

**Complications**—Complications of chickenpox itself are rare except secondary pyogenic infections, such as furunculosis, cellulitis, impetigo and erysipelas. Like other virus diseases, encephalitis and poliomyelitis sometimes occur. Severe involvement of the mucous membranes is uncommon, but occasionally a distressing pharyngitis or laryngitis—the latter may require intubation—is met with. Relapses seldom occur and second attacks are practically unknown.

**Pathological Anatomy**—There are no characteristic anatomical changes in this disease.

**Diagnosis**—As in smallpox, varicella is to be differentiated from other vesicular or bullous lesions, but this is comparatively easy except so far as smallpox itself is concerned. A severe attack of chickenpox may closely simulate a mild attack of smallpox. The description of the two eruptions would seem so distinct as hardly to suggest such confusion, but in practice this is another matter and epidemics of smallpox have been traced to such mistakes.

**Prognosis**—The mortality from this disease is very low, and when death occurs, it can usually be attributed to secondary infections or to some other disease.

**Treatment**—*Prophylaxis*—Isolation of all cases of chickenpox should be continued until the crusts have all disappeared and the individual has been subjected to a series of antiseptic baths. All clothing, bedding and utensils as well as the sickroom itself should be thoroughly disinfected. In institutions convalescent serum has been used to convey a passive immunity with some success.

The active treatment of the patient is that of any other acute infection. The most important objective is preventing the child from scratching the irritating eruption, as this not only aggravates the local condition but may produce secondary infections which lead to scar formation which otherwise does not occur. If the eruption is not too extensive each individual lesion may be painted with equal amounts of tincture of iodine and alcohol. Warm baths twice a day give great relief and are also helpful in preventing secondary infections. As in smallpox the sulfonamides and penicillin are indicated to control the pyogenic infection of the eruption.

### Herpes Zoster

**Synonyms**—Shingles; *zoster*; *zona*.

**Definition**—Herpes zoster is an acute infectious disease which is probably due to a filtrable virus which affects the spinal posterior root and the extramedullary cranial nerve ganglia. It is characterized by a painful vesicular eruption of the skin and mucous membranes.

**Etiology**—Although a virus has not been identified, this probability is supported by the presence of intranuclear inclusions in the cells of the skin lesions and the reported experimental transmission in man. The portal of entry and the way the virus reaches the ganglia are not known. Furthermore the occurrence of symptomatic herpes is in malarial, lobular pneumonia, meningococcal meningitis etc. and its presence in association with lesions about the ganglia have never been explained.

**Diagnosis**—The diagnosis rests upon the adenopathy, splenomegaly, pyrexia and mononuclear leucocytosis. It is to be differentiated from other diseases such as German measles which present a somewhat similar clinical pattern and from acute lymphocytic meningitis. A 'heterophile antibody reaction' (agglutination of sheep's red cells) has been found in the disease (80 per cent) and has been used in diagnosis. It is not absolutely specific.

**Treatment**—The treatment is nonspecific and consists of rest in bed and other procedures indicated in any infectious disease.

### Epidemic Pleurodynia

**Synonyms**—Myalgia epidemica, epidemic transient diaphragmatic spasm, epidemic diaphragmatic pleurodynia, Devil's grip, Bornholm's disease.

**Definition**—Epidemic pleurodynia is a highly infectious and contagious disease characterized by intense paroxysmal pain in the upper abdomen and lower thorax in the region of the diaphragmatic attachment. There is also pyrexia and headache.

**Etiology**—It is a definitely epidemic disease and has been reported from many countries particularly Iceland, Finland, Scandinavia, the Mid Atlantic States, and Ohio, Illinois and Indiana. It is most prevalent during the summer months and over 50 per cent of the cases in epidemics occur in children under fifteen years. The exact cause is not definitely known but some evidence suggests it to be a filtrable virus. The portal of entry is supposed to be through the nasopharynx and it is transmitted by direct contact. There is no evidence to indicate that it is carried in food, drink or by insects.

**Symptoms and Signs**—There are no prodromata and the onset is sudden with pain in the upper epigastrium and lower anterior thorax. This may vary in intensity from a dull ache or distress to the most exquisite agony, particularly in paroxysms. It is intimately associated with the diaphragmatic insertions and is always aggravated by increased respiratory movement as in deep breathing, coughing, sneezing or laughing. Although this symptom is the most conspicuous, pain, tenderness, hyperesthesia and muscular rigidity in other areas may also be detected, indicating systemic dissemination of the virus. With the pain there is also rapid pyrexia reaching  $104^{\circ}$  F. in a few hours. Chills occur in about half the cases. The fever lasts for 24 to 48 hours when the temperature usually returns to normal but this is frequently followed by a recrudescence of both pain and fever. It may run an irregular course for ten to fourteen days. Other symptoms are headache (sometimes intense), prostration, while nausea, vomiting, diarrhea, and tympanitis are particularly common in children. The respirations are shallow and the severe pain may embarrass pulmonary function and lead to cyanosis.

Physical examination sometimes reveals a pleural friction rub. The epigastrium is tender on deep palpation and the lower thorax may be quite sensitive. The leucocyte count may vary from four to twenty five thousand although it is usually within normal limits. A definite eosinophilia, up to 15 per cent may be found during convalescence.

The principal visceral lesions which may be considered as complications are fibrinous pleuritis, fibrinous pericarditis, orchitis and rarely jaundice.

mal sugar content. This phase lasts a week to ten days with gradual recovery although the spinal fluid findings lag behind the clinical signs.

In addition to the meningeal involvement the only other system commonly affected is the respiratory. A bronchitis and bronchopneumonia are not uncommon in the more severe cases and would appear to be an important factor in the few cases in man with a fatal termination.

**Pathology**—There have been very few autopsies in man. In one case with a fatal ending, apparently due to an unusually virulent virus, an interstitial bronchopneumonia was the most prominent feature. In a more chronic case the choroid plexus, ventricular walls and meninges showed marked thickening and infiltration and absence of the arachnoid space over the basal area.

**Prognosis**—This is good as the death rate is almost negligible and sequelae are unknown except for the very occasional hydrocephalus in children.

**Treatment** is entirely symptomatic.

### Acute Mononucleosis

**Synonym**—Glandular fever

**Definition**—This is an acute infectious disease with pyrexia, superficial adenopathy, and a mononuclear leucocytosis.

**Etiology**—There is considerable doubt as to whether this is a specific disease or whether it may not comprise a group of unknown infections as undoubtedly other diseases with a lymphocytosis such as German measles are sometimes confused with it. The cause is unknown although in recent years there have been an increasing number of cases reported in which the *Listeria monocytogenes* has been isolated either from the peripheral blood or from the cerebrospinal fluid. In time such cases may crystallize into a specific disease.

**Symptoms**—The onset of the disease is insidious with pyrexia, pharyngitis or tonsillitis, headache, chills, abdominal pain and sweating. The temperature is irregular and gradually reaches 100° to 101° F. On physical examination the cervical lymph nodes are first enlarged and tender. This is followed by a similar general adenopathy with enlargement of the tonsils and splenomegaly. The tonsils are painful and occasionally definite follicular lacunar, or membranous tonsillitis occurs. The outstanding feature of the disease is the great increase in the mononuclear leucocytes in the circulating blood. They may number as many as 30,000 per c. mm. and there is not only a relative but an absolute reduction in the granulocytes. There has been some discussion as to whether the mononuclear cells are monocytes and in many instances there is no doubt that they are lymphocytes. In those cases identified with *Listeria monocytogenes* large numbers of monocytes are found and it is not unusual for these patients to develop meningeal symptoms and a so-called lymphocytic meningitis may be present. This *Listeria* has been isolated from the spinal fluid of some of these cases.

The anatomical changes are not specific the lymph nodes alone showing considerable hyperplasia. The course of the disease is invariably to recovery. The pyrexia lasts from two to three weeks.

**Diagnosis**—The diagnosis rests upon the adenopathy, splenomegaly, pyrexia and mononuclear leucocytosis. It is to be differentiated from other diseases such as Germinal mesles which present a somewhat similar clinical pattern and from acute lymphocytic meningitis. A "heterophile antibody reaction" (agglutination of sheep's red cells) has been found in the disease (50 per cent) and has been used in diagnosis. It is not absolutely specific.

**Treatment**—The treatment is nonspecific and consists of rest in bed and other procedures indicated in any infectious disease.

### Epidemic Pleurodynia

**Synonyms**—Myalgia epidemica, epidemic transient diaphragmatic spasm, epidemic diaphragmatic pleurodynia, Devil's grip, Bornholm's disease.

**Definition**—Epidemic pleurodynia is a highly infectious and contagious disease characterized by intense paroxysmal pain in the upper abdomen and lower thorax in the region of the diaphragmatic attachment. There is also pyrexia and headache.

**Etiology**—It is a definitely epidemic disease and has been reported from many countries particularly Iceland, Finland, Scandinavia, the Mid Atlantic States, and Ohio Illinois and Indiana. It is most prevalent during the summer months and over 50 per cent of the cases in epidemics occur in children under fifteen years. The exact cause is not definitely known but some evidence suggests it to be a filtrable virus. The portal of entry is supposed to be through the nasopharynx and it is transmitted by direct contact. There is no evidence to indicate that it is carried in food, drink or by insects.

**Symptoms and Signs**—There are no prodromata and the onset is sudden with pain in the upper epigastrium and lower anterior thorax. This may vary in intensity from a dull ache or distress to the most exquisite agony particularly in paroxysms. It is intimately associated with the diaphragmatic insertions and is always aggravated by increased respiratory movement as in deep breathing, coughing, sneezing or laughing. Although this symptom is the most conspicuous pain, tenderness, hyperesthesia and muscular rigidity in other areas may also be detected indicating systemic dissemination of the virus. With the pain there is also rapid pyrexia reaching 104° F. in a few hours. Chills occur in about half the cases. The fever lasts for 24 to 48 hours when the temperature usually returns to normal but this is frequently followed by a recrudescence of both pain and fever. It may run an irregular course for ten to fourteen days. Other symptoms are headache (sometimes intense) prostration while nausea vomiting diarrhea and tympanitis are particularly common in children. The respirations are shallow and the severe pain may embarrass pulmonary function and lead to cyanosis.

Physical examination sometimes reveals a pleural friction rub. The epigastrium is tender on deep palpation and the lower thorax may be quite sensitive. The leucocyte count may vary from four to twenty five thousand, although it is usually within normal limits. A definite eosinophilia up to 15 per cent may be found during convalescence.

The principal visceral lesions which may be considered as complications are fibrinous pleuritis fibrinous pericarditis orchitis and rarely jaundice.

mal sugar content. This phase lasts a week to ten days with gradual recovery although the spinal fluid findings lag behind the clinical signs.

In addition to the meningeal involvement the only other system commonly affected is the respiratory. A bronchitis and bronchopneumonia are not uncommon in the more severe cases and would appear to be an important factor in the few cases in man with a fatal termination.

**Pathology**—There have been very few autopsies in man. In one case with a fatal ending apparently due to an unusually virulent virus an interstitial bronchopneumonia was the most prominent feature. In a more chronic case the choroid plexus ventricular walls and meninges showed marked thickening and infiltration and absence of the richmond space over the basal area.

**Prognosis**—This is good as the death rate is almost negligible and sequelae are unknown except for the very occasional hydrocephalus in children.

**Treatment** is entirely symptomatic.

### Acute Mononucleosis

**Synonym**—Glandular fever

**Definition**—This is an acute infectious disease with pyrexia, superficial adenopathy, and a mononuclear leucocytosis.

**Etiology**—There is considerable doubt as to whether this is a specific disease or whether it may not comprise a group of unknown infections as undoubtedly other diseases with a lymphocytosis such as German measles are sometimes confused with it. The cause is unknown although in recent years there have been an increasing number of cases reported in which the *Listerella monocytogenes* has been isolated either from the peripheral blood or from the cerebrospinal fluid. In time such cases may crystallize into a specific disease.

**Symptoms**—The onset of the disease is insidious with pyrexia, pharyngitis or tonsillitis, headache, chills, abdominal pain and sweating. The temperature is irregular and gradually reaches 100° to 104° F. On physical examination the cervical lymph nodes are first enlarged and tender. This is followed by a similar general adenopathy with enlargement of the tonsils and splenomegaly. The tonsils are painful and occasionally definite follicular lacunar or membranous tonsillitis occurs. The outstanding feature of the disease is the great increase in the mononuclear leucocytes in the circulating blood. They may number as many as 30,000 per cumm. and there is not only a relative but an absolute reduction in the granulocytes. There has been some discussion as to whether the mononuclear cells are monocytes and in many instances there is no doubt that they are lymphocytes. In those cases identified with *Listerella monocytogenes* large numbers of monocytes are found and it is not unusual for these patients to develop meningeal symptoms and a so-called lymphocytic meningitis may be present. This *Listerella* has been isolated from the spinal fluid of some of these cases.

The anatomical changes are not specific, the lymph nodes alone showing considerable hyperplasia. The course of the disease is invariably to recovery. The pyrexia lasts from two to three weeks.

seldom occurs in infants children are not uncommonly infected, but it most frequently develops between the ages of twenty and fifty, and more often in the male than the female. Heredity plays no role in its transmission.

**Symptoms**—The exact incubation period is unknown and its life history is probably almost identical with that of tuberculosis although acute cases



Fig. 66.—Lupular tuberculosis (Courtesy of Dr. Howard Morro, Diseases of the Skin) From Sutton and Sutton



Fig. 67.—Tubercular leprosy (Photograph by Bureau of Science Manila, D. John A. John, Acting Director) From Sutton and Sutton, Diseases of the Skin

are rare. When fully developed the disease is localized most frequently to the skin and mucous membranes or to the nervous system. In some the former predominate and in others the latter but in practically all cases there is some involvement of both. Therefore three principal varieties have been

Such lesions as sinusitis, otitis media, pyelitis, and bronchopneumonia, are most probably due to secondary infections

The pathological anatomy of this disease has never been explored as there have been no autopsies recorded. Abdominal laparotomies have been done through mistal en diagnoses but no abnormal findings have been detected

The diagnosis seldom offers any difficulty in epidemics but, in sporadic cases and in the initial stages of an outbreak this disease is often mistaken for acute peritonitis of the upper abdomen due to perforated peptic ulcer, cholecystitis, acute pancreatitis, etc. It is further confusing in children with pronounced gastrointestinal symptoms. The intensity and paroxysmal character of the symptoms with fever and headache should suggest the proper diagnosis. Other diseases with which it may be confused are acute diaphragmatic pleurisy (pneumococcic, rheumatic or tuberculous), herpes zoster, dengue, etc. Each has its characteristic features, however.

The course of epidemic pleurodynia may vary considerably from a mild, comparatively painless, two days' illness to the most exquisite agony. Recurrences are common and the disease may be prolonged by these for several weeks. The death rate is insignificant, only about a dozen deaths having been recorded in tens of thousands of cases.

**Treatment**—This is purely symptomatic. Bed rest, sedatives, analgesics and strapping the lower thorax and epigastrium to restrict diaphragmatic and intercostal movements offer the best means of making less uncomfortable this painful but not serious disease.

## Leprosy

**Definition**—Leprosy is a specific chronic infectious disease caused by the *Mycobacterium leprae* or *B. leprae*. It has a particular predilection for the mucocutaneous tissues and the peripheral nerves.

**Distribution**—In former centuries leprosy was not only a disease of wide distribution but of high incidence. Partly through persistent and compulsory, although unorganized isolation it has greatly diminished in frequency, although there is probably no country in the world where it has been completely eradicated. It is most common in eastern and southern Asia, the islands of the Pacific and Australasia. In the Western Hemisphere it is most common in the West Indies, Mexico, Central America and the southern countries of South America. In the United States and Canada sporadic cases are seen and in addition there are definite foci in Louisiana, Minnesota, California, and South Carolina.

**Etiology**—The disease is considered to be due to *Mycob. leprae* which is closely related to the tubercle bacillus both in its staining and cultural characters. It can always be recovered from the typical anatomical lesions although as yet the disease has not been artificially transmitted to man or the lower animals. The method of its transmission is also in doubt. The frequency with which the initial lesions are found in the mucous membrane of the nose suggests that it may gain entrance through the nasal mucous membrane. It



smooth and often have the texture of velvet. They are most noticeable on the face, the hands and the feet, about the genital region, and over the lower abdomen and inner sides of the thighs. The pigment of the skin gradually fades and becomes a fawn color. Some of the nodules entirely disappear while others progress in a centrifugal manner until large areas of the skin are involved. The thickening of the skin of the face spreads over the nose, cheeks, the eyebrows—the hair on the outer half of which is lost—about the mouth and into the lobes of the ears, giving to the individual a peculiar mask-like or “leonine” appearance. The skin becomes dry and ichthyotic and sometimes looks like pigskin with the hair follicles open and prominent. The nails are thinned at their bases and may become striated and malformed. Successive crops of the primary erythematous and nodular lesions may involve any part of the skin. Whereas at first they are reddish brown or of a violaceous hue, they soon fade to the dusky brown color described above. While this is the usual course of the lesions, ulceration with loss of tissue also occurs. There may be great destruction of the bones of the nose, pharynx, and larynx with perforation of the palate. The eyes are not infrequently involved leading to keratitis, iridocyclitis and even blindness. These destructive lesions may show healing in some portions, and extension in others. The scar tissue resulting leads to great deformity which not only involves the skin but also the mucous membrane of the pharynx and larynx. Peripheral lesions of the fingers and toes may involve the cutaneous and deeper tissue with local necrosis, loss of substance and absorption of the fingers and toes induced by the trophic effects due to the peripheral nerve lesions.

**Neural or Anesthetic Leprosy**—In addition to extensive and more or less symmetrical cutaneous lesions, there is a definite evidence of neural involvement. The skin lesions in their early stages are erythematous and may simulate erythema multiforme but in time the skin becomes smooth and brownish with a clear cut margin. Vesiculation and superficial ulceration is uncommon.

At first these areas are irritable and hyperesthetic but as time passes they gradually become less so and anesthesia follows. This is parallel to the involvement of the peripheral nerve trunks particularly the ulnar, tibial, posterior cervical and peroneal. On palpation they will be found thickened and nodular and pressure on them elicits no pain. In addition to the anesthesia there is an absence of the sense of touch and of heat and cold. Therefore the part is particularly liable to trauma and burns as in syringomyelia which may lead to extensive ulceration and necrosis. The trophic changes in the skin and muscles now become prominent the thenar and hyperthenar eminences become flattened and the interosseous spaces pronounced from wasting muscles. There are contractures which are most obvious in the upper extremities producing the so called claw or leper hand. The atrophy of the face muscles still further accentuates the mask-like appearance already mentioned.

**Pathological Anatomy**—The essential anatomical lesion of leprosy is a granuloma and in this way closely approximates the more chronic lesions of the tubercle bacillus and *Treponema pallidum*. In fact it is sometimes difficult to be certain of their histological differentiation. The lesion contains

described, the mucocutaneous or nodular type, the neural or anesthetic type, and the mixed type. The last is an unnecessary division and only leads to confusion.

The earliest symptoms are vague and are usually those of any chronic insidious infection, namely, general malaise, headache, debility and various muscular and neuritic pains. Occasionally bouts of pyrexia may be recorded, while rheumatism is quite common and further suggests that the portal of entry



Fig. 508.—Photograph of a case of leprosy showing pronounced thickening of the skin of the face and ears. (Courtesy of Dr. J. L. Todd.)

may be through the nasal mucous membrane. In time the true characteristics of the disease begin to manifest themselves and these may be divided for the sake of simplicity into those of the two major symptom patterns.

**Mucocutaneous or Nodular or Tubercular Leprosy.**—The characteristic lesions are nodular or tubercular. They appear on the skin as reddish brown spots varying from one quarter to several inches in diameter. They are seldom much elevated, but give the impression that the skin is thickened but are

drops, three times daily, in any vehicle which the patient may desire, and must be continued over long periods. In some unfortunates it causes gastric irritation which prevents its use. It may be administered by intramuscular injections. This is usually prepared according to the "Merzdo" formula which is chaulmoogra oil and camphor 60 cc each and resorcin 4 grams 0.3 cc to 1 cc injected intramuscularly two or three times a week. Unfortunately this usually produces local pain. More recently the fatty acids of chaulmoogra oil have been employed, and also the ethyl esters of the fatty acids. These may also be injected intramuscularly, while other combinations have been advised also. The treatment must be continued for several years at least although short periods of intermission may be allowed. As in other infections, the earlier treatment is started in the disease the more gratifying are the results.

Recently promin (sodium p, p' diammodiphenylsulfone N N didextrose sulfonate) and drisone (disodium formaldehyde sulfoxylate diammodiphenyl sulfone) have given encouraging results but still require prolonged clinical trials. The former is given intravenously in doses of 2 to 3 Gm daily in courses of two weeks with a week's interval. The latter may be given by mouth in 0.3 Gm capsules two to three times a day with meals. There should also be a few days rest period every 4 to 6 weeks.

The cutaneous lesions respond quite favorably to x ray therapy, while radium has more recently been employed in lesions of the mouth and eye. Local aseptic measures should be used until the ulcerated areas are healed and sometimes surgical procedures are indicated. The patient should be kept in a cheerful community, and with modern treatment hope should be the watchword. The general handling of the case is similar to that of tuberculosis.

### Toxoplasmosis

Toxoplasmosis is a recently recognized infection due to the genus *Toxoplasma*. The organisms have been recovered from body exudates and fluids but usually are intracellular singly or in clumps in nerve muscle and endothelial cells and in mononuclear polymorphonuclear eosinophile and epithelioid cells. They are minute (2 by 1 to 2 microns) pleomorphic (rounded oval crescentic pyriform or elongated) protoplasmic masses.

The portal of entry is not known. It is accepted however that it can be an intrauterine infection. Under such conditions the principal locus of involvement is the central nervous system. In the postpartum infection the organs involved are usually the lungs the kidneys and the skin.

The pathological process is first in the blood vessels causing an acute arteritis and phlebitis with rapid necrosis and involvement of surrounding tissue with the eventual formation of a granuloma proceeding to calcification. The clinical pattern will depend upon the localization of these lesions. In the pre-natal cases there are signs of advanced encephalitis and hydrocephalus. In the postnatal cases there is pneumonitis necrotic glomerulonephritis and an exanthem resembling that of typhus. Splenomegaly and hepatomegaly with icterus have also been reported.

many epithelioid cells, vacuolated giant cells, connective tissue cells, mast cells lymphocytes, and plasma cells. There is also a characteristic large, ovoid cell which is called the "lepro cell," the exact significance of which is not yet settled. The granulomatous processes may lead to great destruction of tissue. It is commonly serpiginous, leaving distortion with contracting scar tissue.

**Diagnosis**—The advanced cases must be differentiated from tuberculosis, syphilis, blastomycotic disease and in some cases from leucemic infiltration with ulceration. This can be readily accomplished either by biopsy of the infected tissue or direct detection of the *Mycobacterium leprae* in smears, especially from the nasal mucous membrane. In the early stages and particularly in endemic cases, the diagnosis may be attended by some difficulty. There are, however, a number of points which when taken together are of great aid. These are the peculiar fawn or yellowish brown color of the skin which may be either hyperesthetic or anesthetic, and in particular the involvement of the lobes of the ears and the eyebrows, with alopecia of the outer half of the latter. The various skin eruptions may be simulated by syphilis, and unfortunately for the differential diagnosis, the Wassermann reaction is frequently positive in nonsyphilitic lepers. Syringomyelia is the principal disease to be eliminated in the purely neural type.

**Prognosis**—Until the last generation leprosy was looked upon as a hopeless disease but recent advances in its therapy have changed this from gloom to hope. The disease is chronic and may extend over many years but eventually the mutilating deformities make the patient a piteous sight. Fortunately not all are so afflicted and may live to an advanced age without distress or tissue destruction dying of some entirely different disease.

**Treatment—Prophylaxis**—The nasal and nasopharyngeal discharges, and the exudate from cutaneous ulcerating lesions harbor the virus of this disease. Therefore such materials and articles which they may contaminate should be destroyed. It is best that patients with open lesions be segregated, and this has been done in many countries where they are housed at government expense in leper colonies. Such isolation has undoubtedly been an important if not primary factor in the localization of this disease and the great decline of its incidence. Its similarity to tuberculosis would suggest that this would be a proper method to control this latter disease and in fact this has been successfully demonstrated in many areas but the accomplishment of these public health measures in tuberculosis has not been assisted by the same fear of the disease the "outcast" and the "unclean" being synonyms of the leper from biblical times.

The neural type without nasal or nasopharyngeal ulceration may be looked upon as "closed" cases but before they are allowed to mingle in society it should be clearly demonstrated that *Mycobacterium leprae* are not present in the nasal secretions even though no macroscopic lesion is evident but to be on the side of safety these cases should also be quarantined until the urine and feces have been thoroughly examined as it is well known that they may contain the bacilli.

The active treatment of leprosy rests principally upon the use of chaulmoogra oil and its derivatives. The pure oil may be given by mouth 5 to 60

legs and forearms. They are extremely painful and tender and soon assume a purplish and then a yellowish color before they disappear after a period of several days or weeks. They may recur in crops. They were at one time identified with rheumatic fever (see page 67) but in recent years have also been considered as an allergic evidence of primary tuberculosis. Although most frequently associated with these two diseases they have also been found with nonspecific streptococcal infections with syphilis and with other organisms. It cannot be considered as a specific lesion but rather as an allergic reaction most frequently indicative of the first two diseases.

**ERYTHEMA MULTIFORME.**—Obviously a most diverse type of erythema which not only assumes many and varied characteristics but appears both on the skin and mucous membranes. Its cause is unknown although the prevalent ideas of focal infections and intestinal intoxications have held a popular place. It may simulate syphilis ringworm pemphigus pityriasis, lupus erythematosus etc. In fact it is a protean sign of multitudinous etiologies and not a specific disease.

### **Lupus Erythematosus Disseminatus**

**Synonyms**—*Ulcerythem centrifugum* *Schorrhea congestiva*

**Definition**—Lupus erythematosus is a systemic disease characterized at some time in its course by an erythematous eruption usually on the face and scalp. There are also various vascular and other visceral lesions which indicate its systemic character. It has not been proved as tuberculous, and it is unfortunate that the term 'lupus' has been identified with it as it is quite distinct from 'lupus vulgaris'.

**Etiology**—Some claim that it is due to tuberculosis while others name the streptococcus. This is a fairly common claim for a number of diseases (see *Erythema nodosum*). There is one important factor in its etiology which must be emphasized namely that sunlight or ultraviolet light seem at times to initiate the disease. Females in the third and fourth decades are principally affected and males seldom.

**Symptoms and Signs**—The onset is most irregular as almost any of the features to be described below may first cause the patient to seek medical advice. In spite of the bizarre and irregular manifestations the true diagnosis may be arrived at before the typical skin lesions appear. These however may be transitory or long delayed leading to continued confusion.

The onset may be either insidious or explosive and there may be a preceding history of Raynaud's disease like lesions in the fingers. With the insidious onset there is fatigue and exhaustion low fever and joint pains which may lead to confusion with rheumatoid arthritis or rheumatic fever. In time the skin lesions may appear or be preceded by signs of visceral disease. With the acute onset the constitutional and skin lesions may appear together with high fever and great prostration.

**Skin Lesions**—The most characteristic lesion is a symmetrical dermatitis over the nose and cheeks with edema of the eyelids. The lesions may appear elsewhere as bright reddish violet papillary or bulbous with petechiae or purpura. With involution there may be pigmentation similar to that of Ad

The neurologic signs are quite diverse including those of internal hydrocephalus, bilateral choroiditis, hyperactive reflexes, Babinski's sign, spastic contractions, nystagmus and convulsions. In survivors there is impaired vision and defective mental development. The spinal fluid is xanthochromic with a cellular content of 1000 or more chiefly lymphocytes. The clue to the correct diagnosis is found through the x-ray revealing the calcified granuloma.

Although the prognosis is always grave as to life and future disabilities, there are undoubtedly asymptomatic cases recognized accidentally by x-ray or at postmortem. There has now been developed by Warren and Sabra a complement fixation test which is most helpful in the early stages of the disease if it be suspected.

The treatment is symptomatic for the present, although certain of the sulfonamides may be helpful.

### ERYTHEMATOSES

Erythema is due to dilatation of the superficial capillaries and appears either in localized areas or as a general phenomenon, as in scarlet fever. It would not properly be included in a text on internal medicine if it did not present the principal evidence in a group of little understood but apparently systemic diseases. On the other hand erythema is simply a sign which in the older nosography was sometimes elevated to a position of a specific disease. With our present day method of analyzing cause and effect and making diagnoses from factual evidence erythema becomes a sign as do purpura and many other dermatological manifestations. It has frequently associated with it swelling or edema, heat, itching, tenderness and pain but these are not necessarily present thus erythema serves as a lead in diagnosis rather than as an entity unto itself. It would seem that the time has arrived when the skin manifestations of systemic disease should be described even in a single volume as they comprise a large and important realm of medicine and would undoubtedly contribute to a better understanding of the physiology and pathology of both.

The erythemas are often of importance as they may be symptomatic of some external or internal cause. The former are usually contact irritations such as nettles, poison ivy, heat, pressure, x-rays, turpentine, mustard, cantharides, etc. The internal cause is ingestion or inhalation of a wide variety of substances to which the person may be allergic (see page 1441). In addition there are certain drugs which may give a similar reaction the following are the more important—atropine, belladonna, quinine, salicylates, chloral, barbiturates, sulfanilamide and its derivatives, etc. The first two give an erythema on account of a specific pharmacological effect while in the rest the effect is due to an idiosyncrasy and is usually called erythema medicamentosum and may produce a multitude of other skin manifestations.

In addition there are a few types of erythema which would seem to have a more specific systemic indication.

**ERYTHEMA NODOSUM**—This is a rather specific type of lesion characterized by circumscribed indurated erythematous areas on the extensor surfaces of the

but numerous thromboses. A false positive Wassermann reaction is frequently found. Enlargements of the spleen and liver are usual findings and thrombotic necrosis of the former has been recorded.

**Cardiovascular System**—The vascular lesions which have been recorded with increasing frequency as an important visceral feature of this disease may be the essential clue to its real pathological identity including the skin. There may be ischemic lesions of the fingers and toes resembling Raynaud's disease (see page 464). But these vascular lesions are more characteristic in the kidneys where the glomerular tufts are principally involved. It has been difficult to be certain as to the nature of these lesions but the usual appearance is that of hyalinization of the arterioles and round celled infiltration about them. This often leads to renal failure with the usual urinary and blood chemistry findings. There is sometimes hypertension with cardiac hypertrophy which may be independent of a verrucose endocarditis with mitral and aortic insufficiency. The endocarditis (Libman's) is not clinically specific but occurs too often to be a coincidental lesion. Vascular lesions are also found in the retina in the form of small hemorrhages and exudate independent of renal lesions and hypertension. There may also be focal vascular changes in the central nervous system which may produce a variety of clinical signs. Purpura and a Rumpel-Leede reaction are common. In addition to these disseminated vascular lesions involvement of the serous membranes especially pleuritis and pericarditis is frequently encountered. These may pass through the complete cycle of serous inflammation from fibrinous exudate to effusion.

**Pathology**—The pathological features of this disease are chiefly in the histological findings. It may be taken as an example of the so called 'collagen diseases' in which group can be included scleroderma, dermatomyositis and periarthritis nodosa. In fact some pathologists would also include allied diseases rheumatic fever, rheumatoid arthritis and malignant nephrosclerosis.

The typical lesion is found in the small blood vessels throughout the body but principally in those of the kidneys, heart, lungs, liver and serous membranes. There may be little macroscopic evidence of this but microscopically there is fibrinoid degeneration of the collagen or fibrous connective tissue which is characterized by straightening and thickening of the collagen fibers, increased friability, smudged eosinophilic staining and increase of the ground substance. There is also a cellular infiltration surrounding the vessels and finally fibrosis leading to thrombosis and obliteration of the lumen with at times rupture of the vessels.

**Diagnosis**—This is most difficult without the skin lesions to point to the truth and even these may be confusing. A biopsy of the skin may help but even with this and it may be difficult to differentiate from scleroderma, dermatomyositis and periarthritis nodosa. It may be confused with rheumatic fever, rheumatoid arthritis, subacute bacterial endocarditis, acute and chronic nephritis, essential hypertension, granulocytopenia and a number of other visceral lesions.

**Prognosis**—The course of the disease is proverbially uncertain. The arthralgia, pyrexia and general debility may long antedate the skin lesions

dison's disease. These lesions appear chiefly on the exposed surfaces. The finger tips are often first involved but they may be found also on the torso.

There have been described three varieties: (1) symmetrical erythema, (2) local atrophic erythematosis, (3) exanthematous erythematosis. The first and third are probably identical and their distinction is artificial in relation to the systemic quality of the disease. It is not within our present province to enter into the discussion as to whether atrophy of the skin is essential to distinguish these lesions because the significance of the skin lesions is to give a lead to the internist as to the systemic disease with which he has to deal.

**SYSTEMIC FEATURES**—The onset may coincide with an acute pharyngeal infection or may be preceded by a moderate to severe sunburn. In fact with the present popular use of ultra violet rays some cases may date from its use. It is difficult to correlate these physical agents with the initiation of the visceral lesions.



FIG 509.—Lupus erythematosus (seborrheic type). (Courtesy of Dr. Grover W. Wende. From Sutton and Sutton: Diseases of the Skin.)

*Arthralgia* or *exudative arthritis* with myalgia and vague pains is common not only as an initial complaint but also during the course of the disease. Indeed acute rheumatic fever may be the diagnosis for many months and the condition may be treated accordingly, particularly is this the case when endocarditis and serous membrane lesions develop (see below).

The findings in the *blood* are most interesting. There is usually a leucopenia, which may be quite alarming when as low as 1 000 per mm. This, however, is not constant as a moderate leucocytosis has been recorded, but this is usually associated with a secondary infection. Anemia is sometimes conspicuous but is not at all distinctive. Thrombocytopenia has frequently been reported and it has been suggested that this is not primary but is secondary to the vascular lesions in which the thrombocytes are entrapped leading to minute



- Durand, I., Giroud, I., Larrive, F., and Mestrallet, A. *Études sur la maladie des porchers (maladie de Bouchet)*, Arch Inst Pasteur le Tunis 26 213-217 2-3 249 June 1934.
- Dyer H. F., Rumreich A. and Balger I. E. A Virus of the Typhus Type Derived from Fleas Collected from Wild Rats Pub Health Rep USPH Service 46 No 7 744 1931.
- Engle H. and Magnusson H. J. The Phagocytic Activity of Leucocytes in the Rat in Fever Induced in Rats and Mice Pub Health Rep 39 573 1934.
- Faut F. C., Wright W. H., McMullen D. B. and Hunter G. W. III The Diagnosis of Schistosomiasis Japonica I The Symptoms Sign and Physical Findings in Schistosomiasis Japonica Am J Trop Med 26 87 1931.
- Fischer A. E. Herpes Zoster and Disseminated Vesicles (Varicella) J Mediat 2 501 1933 An excellent résumé.
- Fordyce J. A. and Wise E. Leprosy in New York City, Arch Dermat & Syph 11 1 1933.
- Forster R. Zur Serodiagnose der Gonorrhoe und ihrer Verwerthbarkeit in der Praxis Munchen, med Wchnschr 77 187, 1930.
- Fox L. Tularemia A Summary of Certain Aspects of the Disease Including Methods for Early Diagnosis and the Results of Serum Treatment in 600 Patients Medicine 19 1 1940.
- Francis, E. The Occurrence of Tularemia in Nature as a Disease of Man Pub Health Rep 36 1731 1931.
- Francis E. History of Tularemia—DeLamar Lectures—Johns Hopkins University Series 1926 27 pp 94 110.
- Francis E. A Summary of Present Knowledge of Tularemia Harvey Lectures Series 19 7-8 pp 33-48 Harvey Society of New York Medicine 7 411 1923.
- Francis E. and Callender G. R. Tularemia the Microscopic Changes of the Lesions in Man Arch Path & Lab Med 3 517, 1937.
- Francis, E. J. J. A. M. A. 99 10 1937 Tr A Am Physicians 47 143, 1932.
- Francis T. Jr. Studies on Pathogenesis and Recovery in Erysipelas J Clin Investigation 11 2-1 1939.
- Fraser A. R. Metastatic Complications of Gonorrhea and Their Treatment J Urol 8 49 192.
- Frothingham C. L. and McClure C. W. Glaniers Oxford Medicine Vol 5 p 180.
- Futaki K., et al. The Cause of Rat Bite Fever J Exper Med 23 249 1910.
- Galloway I. A. and Elford W. J. Brit J Exper Path 12 40 1931.
- Goodpasture E. W., and House S. J. The Pathologic Anatomy of Tularemia in Man Am J Path 4 213 1928.
- Graham H. J. Trop Med 6 209 1900.
- Graham J. H. Lancet 2 703 1915.
- Graves A. M. Tetanus in New Orleans an Analysis of 813 Cases Ann Surg 92 10 5 1900.
- Hazen H. H. Syphilis St Louis 1920 The C. V. Mosby Co.
- Hegner H., Foot F. M. and Augustine H. L. Animal Parasitology New York 1909 The Century Co.
- Hoare C. A. Cutaneous Leishmaniasis (A Clinical Investigation of Recent Russian Work) Trop Dis Bull 41 371 1944.
- Hollmann H. T. The Fatty Acids of Chaulmoogra Oil in the Treatment of Leprosy and Other Diseases Arch Dermat & Syph 5 94 1920.
- Hollins H. and Denney O. E. Leprosy in the United States J A. M. A. 92 3 1929.
- Hulson E. H. and Young A. L. Syphilis in the Euphrates Arab Am J Syph 16 447 1930 and 17 10, 1930.
- Hurst E. W. and Pawan J. L. Rabies Myelitis I Path & Bact 35 301 1930.
- Jeanneret Minkine M. Le Typhus Exanthématique Paris 1915 Librairie Payot & Cie.

when a positive diagnosis may be made. After this there may be repeated remissions or it may run its course in a few months. The terminal stages are usually characterized by bronchopneumonia but other cases may develop a nonspecific toxemia, cerebral signs, circulatory failure, or renal failure.

**Treatment**—This is highly ineffective although bismuth has been advocated. At least it seems to do no harm, which is more than can be said for gold therapy, x-ray, sunlight and ultraviolet therapy, all of which are strictly prohibited. Until the cause and pathogenic pattern of this disease are known speculative therapy may do more harm than good. Cautious general symptomatic therapy is therefore the best course to pursue.

### References

- Amos H. L. and Birkhaug K. Observations on Experimental Erysipelas. *Tr. A. Am. Physicians* 40: 5, 1925.
- Anderson J. F. Spotted Fever (Tick Fever) of the Rocky Mountain. *U. S. Pub. Health and Marine Hosp. Service Hygienic Laboratory Bulletin*, No. 14, 1903.
- Arkwright I. A. and Bacot A. W. Investigation of the Etiology of Typhus Fever, Especially Undertaken for the Egyptian Government in the Public Health Laboratories. *Cairo Brit. J. Exper. Path.* 4: 70, 1923.
- Ash W. F. et al. Weil's Disease. A Complete Review of American Literature and an Abstract of the World Literature. *7 Crce. Reports Medicine* 20: 145, 1941.
- Badger L. F., Dyer R. E. and Rumreich A. An Infection of the Rocky Mountain Spotted Fever Type. Identification in the Eastern Part of the United States. *Pub. Health Rep., USPH Service* 46: 463, 1931.
- Dates L. B., Dunn L. H. and St. John J. H. Relapsing Fever in Panama. The human tick *Ornithodoros* taylori demonstrated to be the transmitting agent of relapsing fever found in Panama. *Am. J. Trop. Med.* 1: 183, 1921.
- Bernstein A. Infectious Mononucleosis. *Medicine* 19: 8, 1940.
- Bhattacharya U. A Treatise on Kala-azar. London, 1928.
- British Trench Fever Commission. *Brit. M. J.* 1918.
- Butler C. M. Primitive Syphilis. *U. S. Nav. M. Bull.* 26: 333, 1928.
- Chipman E. D. The Etiology and Treatment of Leprosy. *J. A. M. A.* 65: 934, 1915.
- Citron, J. Die Syphilis. *Spec. Path. u. Therap. Inn. Krankheiten* Bd. 2, Berlin, 1910. Urban & Schwarzenberg.
- Cleland J. B. and Bradley B. Report of the Director General of Public Health. New South Wales, 1916-18.
- Coggeshall I. T. Filariasis in the Serviceman. *Retropect and Prospect J. A. M. A.* 1: 131, 8, 1940.
- Councilman and Associates. Studies on the Pathology and Etiology of Variola and Vaccinia. *J. Med. Res.* 6: 8, 1904.
- Craig C. E. A Manual of the Parasitic Protozoa of Man. Philadelphia, 1926. J. B. Lippincott Co.
- Crookshank E. M. History and Pathology of Vaccination. 2 Vols. H. W. Lewis, London, 1889. The second volume contains reprints of Jenner's four publications.
- Danielopolu D. Le Typhus Exanthematique. Bucarest, 1919. Ch. Gobli.
- D'Aunoy R. and Beven J. L. Antirabic Vaccinations at Charity Hospital of New Orleans for Years 1929-30. *Am. J. Clin. Path.* 1: 333, 1931.
- Deaderick W. H. A Practical Study of Malaria. Philadelphia, 1909. W. B. Saunders Co.
- Divinelle F. H., Rein C. R., Sternberg T. H. and Shelton A. J. Preliminary Report of Evaluation of Ipecillin in the Treatment of Yaws. *Am. J. Trop. Med.* 26: Mar. 1946.
- Duff C. Lyman. The Diffuse Collagen Disease. A Morphological Correlation. Annual Lecture. Royal College of Physicians (C. A. M.), 1941.

- Moore F F Penicillin in the Treatment of Syphilis Supplement to the Modern Treatment of Syphilis ed 2 Springfield 1941 Charles C Thomas
- Mooser H Castaneda M R and Zimmer H Rats as Carriers of Mexican Typhus Fever J A M A 97 231 1931
- Napier L E Kala-azar 1927 Oxford University Press London, ed 2
- Nattan-Larrier L Infiltration du spirille de la fièvre récurrente à travers les teguments et les muqueuses intactes Bull Soc Path 1909 Exot 239
- Neuer J Eine Hautreaktion zum Nachweis gonorrhoeischer Tiefenerkrankungen Wien klin Wchnschr 45 398 1932
- Nichols H J J A M A 55 216 1910 J Exper Med 12 616 1910 loc cit 14 196 1911 Am J Trop Med 5 4-9 1928
- Nicoll W Recent Progress in Our Knowledge of Parasitic Worms Parasitology 6 141 1913 14
- Noguchi H The Pure Cultivation of Spirochaeta Duttoni, etc J Exper Med 16 109 1912
- Parker R R Spencer R R and Francis L Fularemia Infection in Ticks of the Species Dermacentor Andersoni Stiles in the Bitter Root Valley Montana Pub Health Rep 39 1057 1934
- Peritucci L A Tetrasporon Am J M Sc 209 4 1914
- Pfeiffer L Jahrb f Kinderheilk 21 2 1883
- Polak H J Arch f Schiffs u Tropen Hyg 31 330 1934
- Pollitzer S Historical Sketch of Leprosy in the United States J Cutan Dis 29 261 1911
- Reed A C Anderson H H David N A and Leake C D Carlarsens in the Treatment of Amebiasis J A M A 98 155 1932
- Regan J C Advantage of Serum Therapy as Shown by a Comparison of Various Methods of Treatment of Anthrax Am J M Sc 162 406 1931
- Report of British War Office Trench Fever Investigation Committee Oxford Press London 1919
- Report of Commission of American Red Cross Research Committee Trench Fever New York 1918 Oxford University Press
- Ricketts H T Contributions to Medical Science by Howard Taylor Ricketts 1870 1910 Chicago 1911 University of Chicago Press
- Rivers T M Skin Infection of Rabbits with Hemolytic Streptococci Isolated from Patients with Erysipelas Method of Demonstrating Protective Action of Immune Sera J Exper Med 41 179 1923
- Robertson A Causal Organism of Bat-bite Fever in Man Ann Trop Med 11 157 1924 Spirillum minus Carter 1887 Aetiological Agent of Bat-bite Fever, Review Ann Trop Med 24 367 1930
- Ross H An Intracellular Parasite Developing into Spirochaetes Brit M J 2 1651 1912
- Rusnell P E West I A and Van H E Practical Malariaology Philadelphia 1946 W B Saunders Co
- Sakamoto H I Diagnosis of Glanders J Immunol 18 331 1930
- Santee H E Anthrax and Its Treatment Ann Surg 78 3-6, 1923
- Schanberg J Diseases of the Skin and Eruptive Fevers ed 4 Philadelphia, 1921 W B Saunders Co
- Schohl O Further Experiments Concerning Immunity in Treponematosus Infections Philip pine J Sc 45 1931 Ibid 46 15 17 183 1931
- Schohl O and Miyao I Immunologic Relation Between Yaws and Syphilis Phil Jour Science 40 89 and 91 1930
- Sellards A W Goodpasture E W and DeLeon W Investigations Concerning Yaws, Philippine J Sc 22 219 233 251 285 1933
- Selwyn Clarke P LeFauu G H and Ingram A Relapsing Fever in the Gold Coast Ann Trop Med and Parasit 17 389 1933

- Jenner E. *An Inquiry into the Causes and Effects of the Variolæ Vaccinæ*, London, 1798, Sampson Low, No 7 Berwick St, Soho, Facsimile Edition Lier & Co Milan, Italy, 1923, Further Observations on Variolæ Vaccinæ A Contribution of Facts and Observations Relative to the Variolæ Vaccinæ The Origin of the Vaccine Inoculation
- Jergen G. *Das Fleckfieber* Berlin, 1916 A Hirschwald
- Keefer, C S and Spink, W. Studies of Haemolytic Streptococcal Infection III. The Characteristics of the Haemolytic Streptococci Isolated from Patients With Erysipelas, *J Clin Investigation* 16 155 1937
- Kissmeyer M A. *La Maladie de Boeck*, Paris, 1932, Masson et Cie
- Klumperer I. Lollach A D and Baehr, C. Acute Disseminated Lupus Erythematosus and Diffuse Scleroderma *J A M A* 119 331 1942 *Arch Path* 32 569, 1941
- Knowles R and Das Gupta B M. Rat bite Fever as Indian Disease *Indian M Gaz.* 63 491 1928
- Kolle and Wassermann. *Handb d path Mikroorganismen* 4 253, 1928
- Kristjansen, A. Die Komplementbindungs Reaktion bei Gonorrhoe, *Arch f Dermat u Syph* 164 239 1931
- Lenhartz, H. Erysipelas, Nothnagel's Encyclopedia of Practical Medicine American Ed., Philadelphia 1902, W B Saunders Co
- Lenhartz H. Die Septische Erkrankungen Nothnagel's Spezielle Path u Therap, Vienna, 1903
- Lille R D. Pathology of the Eastern Type of Rocky Mountain Spotted Fever, *Pub Health Rep USPH Service* 46 2840, 1931
- Lloyd B J. Plague—Past Present and Future *J A M A* 85 729 1925
- Löffler and Frosch. *Centralbl f Bakt* 23 256, 1897
- Longcope, W F. Infectious Mononucleosis (glandular fever) *Am J M Sc.* 164 181 1922
- Lubrs, E. *Reitz Handb d path Mikroorganismen*, Kolle, Kraus, Uhlenhuth, Berlin 6 1 1929
- McCoy G W. Antirabic Vaccine Paralysis *Pub Health Rep* 45 1888 19 0
- McCoy G W. Utility of Antiplague Vaccines and Serums, *U S Pub Health Rep* 45 1647 1920
- McCoy G W, and Chapin G W. Bacterium Tularensis the Cause of a Plague like Disease of Rodents, *USPHS Pub Health Bull* 53, Jan, 1912, p 21
- McKendrick A G. Analytical Review of Reports from Pasteur Institutes etc *Quart Bull Health Organ.* 1 110 1932
- Mackie F P. The Part Played by Pediculus Corporis in the Transmission of Relapsing Fever *Brit M J* 2 1706 1901
- Mackie F P. A Preliminary Note on Bombay Spirillar Fever, *Lancet* 2 83<sup>n</sup> 1907
- Mackie Fhos L et al. *Manual of Tropical Medicine* Philadelphia 1941 W B Saunders Co
- Manson Bahr, P H. *Manson's Tropical Diseases* ed. 11 1929, Nord Cassell & Co
- Manson Bahr P H. *Manson's Tropical Diseases* London 1929, Cassell & Co p 210, ed 9
- Maxcy, K. F. An Epidemiological Study of Endemic Typhus (Brill's Disease) in the Southeastern United States with Special Reference to Its Mode of Transmission *Pub Health Rep USPH Service* 41 No 52 2967 1926
- Medical Department of the United States Army in the World War 9 463, 1919
- Medical Research Committee. The Laboratory Diagnosis of Gonococcus Infections Special Report Series No 19 1918
- Mendelson R W. *Glanders* *J A M A* 93 1379, 1929
- Miller R H. Report on 116 Cases of Tetanus *Surg Gynec Obst* 36 90 1923
- Miyake H. Mittl und Grenzgeb d Med u Chir 5 231 1894 1900
- Moore J E et al. Treatment of Cardiovascular Syphilis *Arch Int Med* 49 8.9 1932.
- Moore, J E, et al. Venereal Disease Information *U S Public Health Service The Management of Syphilis in General Practice* 10 No 19-9 Cooperative Clinical Studies in the Treatment of Syphilis 13 Nos 4 11 7 1932

## CHAPTER XX

### CHEMOTHERAPY AND ANTIBIOTICS

**Definition.**—For nearly one hundred years it has been an ambition of pharmacologists to produce chemical agents which would have a bactericidal or bacteriostatic influence on specific organisms pathogenic to man and to domestic animals. Primitive examples are found in mercury as a spirocheteicide in syphilis before the *Treponema pallidum* was discovered, ipecacuanha was used for amebiasis long before emetine was found to be a relative specific and quinine was known to be an almost certain antagonist to the *Plasmodium malariae*. These are but a few examples of the shrewd therapeutics of history to which might be added the physiological and nutritional empiricisms such as digitalis in cardiac failure and citrus juices and even slippery elm as an antidote to scurvy. Many of man's hopes for the prevention and antagonism to disease or abnormal states have been rewarded by spectacular successes. In addition to the above there are the triumphs of substitution therapy as in the combat against hypothyroidism, diabetes, pernicious anemia, Addison's disease, etc. In all of these and other diseases including infections, food and organismal deficiencies there has been the ambition to seek a specific cure or remedy and to a large degree this has been successful.

When one considers the infectious diseases in their broadest scope the noxious agents have been so many and diverse in a biological sense including, filtrable viruses, rickettsia, bacteria, spirochetes, spirilla, plasmodia, protozoa, etc. that the range for specific remedies would seem almost infinite. But still the quest goes on by determined effort, consummate patience and courage with real hazards as has been shown by the number who have fallen by the agents of the diseases that they were striving to conquer.

It has long been known that products of certain bacteria, molds and other lower forms of life were beneficial or helpful in the growth of others of the same higher or lower species. These became known as biotic substances. It was also known that there were produced on the contrary substances that were antagonistic to the growth and survival of these same and other species. These were known as antibiotics. There are many of these which have been successfully demonstrated *in vitro* but have been found to be too toxic for use in laboratory animals and finally impracticable in man. Therefore the range of antibiotics in the combat against human diseases has been limited in number but fortunately not in the variety of bacteria and other organisms which are causative of diseases.

The chemotherapeutic agents and antibiotic substances have a common purpose and general action. Therefore it would be profitable and proper to discuss them both under a common designation.

The number of chemotherapeutic agents are rather numerous when we consider the arsenicals, bismuth, mercury, quinine, iabaine, emetine, anti-

- Siler J F Hall M W, and Hitchens A P Dengue, Manila, 1926, Bureau of Printing 1926
- Simpson W M Tularemia a Clinical and Pathological Study of Forty eight Non fatal Cases and One Rapidly Fatal Case with Autopsy, Occurring at Dayton, Ohio, Ann. Int Med 1 1007, 1928
- Solomon, H Berh, A et al The Use of Sodoku in the Treatment of General Paralysis Arch Int Med 38 391 1926
- Spencer R R and Parker R B Rocky Mountain Spotted Fever, Vaccination of Monkeys and Man, Public Health Rep Treasury Dept 40 No 41, 1925
- Sprunt, T P, and Evans E A Mononuclear Leucoeytosis in Reaction to Acute Infections (infectious mononucleosis), Bull Johns Hopkins Hosp 31 410, 1920
- Stannus, H S Brit J Ven Dis 4 64, 1928
- Stitt, E H The Diagnostics and Treatment of Tropical Diseases ed 5, Philadelphia 1929, P Blakiston a Son & Co
- Stokes J H Modern Clinical Syphilology Philadelphia, 1927 W B Saunders Co
- Stone W J The Treatment of Tetanus, J A M A 78 1919 1922
- Strong, R P Philippine J Sc 5 433 1910 Atlantic Med J 1 47, 1926 Medical Report of the Rice Harvard Expedition to the Amazon, 1926, Report of the Harvard African Expedition, 1930
- Strong H P Studies on Pneumonic Plague and Plague Immunization Philippine J Sc Section B 7 129 1912
- Strong, R P et al Report of the International Plague Conference Held at Mukden, April 1911, Under the Auspices of the Chinese Government Bureau of Printing, Manila 1912 p 135
- Swift H The Harvey Lectures 82 1919 20
- Symmers D The Antitoxin Treatment of Erysipelas Results of 705 Cases at Bellevue Hospital J A M A 91 555, 1928
- Symmers D The Serum Treatment of Anthrax Septicemia, Ann Surg 75 163 1922
- Symmers D and Cady D W The Occurrence of Virulent Anthrax Bacilli in Cheap Shaving Brushes J A M A 31 2120 1921
- Thayer T E H Cardiac Complications of Gonorrhea Bull Johns Hopkins Hosp 33 361 1925
- Thayer W H Lectures Upon the Malarial Fever New York 1907
- Thayer W S and Hewetson A Malarial Fevers of Baltimore Rep Johns Hopkins Hosp 1895
- Tileston W Septicemia, Oxford Medicine New York 4 895 1921
- Tropical Diseases Bulletin Vol 1 1912 Tropical Diseases Bureau London (Abstracts of current literature since 1912)
- Tropical Diseases Bulletin Abstracts of Literature on Plague
- Tunnichiff, R Further Studies on Specificity of Streptococci J A M A 75 134 1920
- Ude W H and Platon E S Treatment by Radiation J A M A 95 1 1930
- Wainwright J M Incidence and Treatment of Tetanus Arch Surg 12 1063 1925
- Warren J and Rubin A B The Complement Fixation Reaction in Toxoplasmosis Proc Soc Exper Biol & Med 51 11 1943
- Williams C L The Diagnosis of Human Plague J A M A 75 370 1920
- Wolbach S B Studies on Rocky Mountain Spotted Fever J Med Res 41 1 1919
- Woodward, S B Argument on Vaccination before the Committee on Public Health of the Massachusetts Legislature New England J Med 202 102 1920
- Young C W Kala azar in China China M J 37 797 1923
- Zuelzer, W W Infantile Toxoplasmosis Arch Path 38 1 1944



mony salts etc. But in this chapter there will be considered only the sulfonamides and the antibiotics—penicillin streptomycin etc.

In 1935 when Dormig published his experiments showing that 4' sulfamido 2,4 diamino azo benzene had a spectacular effect on hemolytic streptococcal infections in mice a new era in chemotherapy was born. A few months later the Trefouels and associates pointed out that para aminobenzenesulfonamide was apparently the active part of the compound with which Dormig had worked. There soon followed many clinical reports of the value of the original compound and its soluble derivative the disodium salt of 4' sulfamido phenyl 2,4,7 acetyl amino 1 hydroxy naphthalene 3,6 disulphonic acid. Much confusion was created by the number of trade names given to this compound some of which were prontosil prontylin stamid, streptocide colsulnyde and prontosil album. It was suggested to the Council of Pharmacy and Chemistry that the nonproprietary name of "sulfanilamide" should be adopted. This was accepted as it denoted the composition and was also being used abroad. Since then other compounds have been brought into use such as sulfapyridine sulfathiazole sulfadiazine and sulfaguanidine. On account of the number of these compounds and the prospect of still others the inclusive name of "sulfonamides" has been adopted to indicate these forms of chemotherapeutic agents in general.

In 1929 Fleming published an account of an active agent obtained from a certain type of *Penicillium* which had a powerful bacteriostatic action on certain pyogenic cocci. It was given the name of penicillin. Further work revealed that this agent could be found in the filtrate of broth cultures of the *Penicillium notatum*.

In 1942 Florey and Jennings established a unitage for this substance. This is known as the Oxford unit. It is the amount of penicillin which when dissolved in 50 c.c. of meat extract broth just inhibits completely the growth of a test strain of *Staphylococcus aureus*. The work of Fleming and its confirmation by Florey stimulated anew the search for antibiotics that could be used in man. Several scores of antibiotic substances have so far been produced but of all these streptomycin streptothricin aureomycin and chloromycetin are the only ones in addition to penicillin that have been found to be sufficiently nontoxic to have a therapeutic value in man. Streptothricin is produced by the growth of *Streptomyces lavendulae*, streptomycin from *Streptomyces griseus* and aureomycin from *Streptomyces aureofaciens*. To the present the reports on the clinical use of streptothricin have been few. It has been found both in vitro and in vivo in experimental animals to be effective against gram negative bacteria. In fact streptothricin and streptomycin have almost identical therapeutic effects but a much greater amount of clinical work has been done with streptomycin. The streptomycin unit (S.U.) is the amount of material that will inhibit the growth of *Esch. coli* in 1 c.c. of medium equivalent to 1 m.u. of streptomycin base.

**Bacterial Effect**—The action of sulfonamides and antibiotics upon bacteria is in most part bacteriostatic although they may have variable bactericidal actions. These effects in the main therefore prevent the multiplication of the organisms within the tissues and tissue fluids permitting their destruc-



important effect upon the intestinal bacteria and consequently is particularly efficacious in such dysenteric infections. It has been used with good effects in intestinal and particularly colonic operations. Sulfanilamide on account of its solubility is of special value for topical application to open wounds or superficial dressings. It must be stated here that certain individuals show a considerable impairment of absorption and this must always be borne in mind when expected blood levels are not reached with standard doses.

Penicillin is readily soluble but unfortunately is rapidly destroyed in the acid medium of the gastric contents. This however is quantitative. If sufficiently large amounts are given significant blood levels may be reached. There would appear to be a number of factors which vary from individual to individual that make this method of administration open to chance. It will however be the ideal method when these problems are mastered.

Streptomycin is also readily soluble and can be given by mouth, but it is absorbed very slowly and a great amount so given can be recovered in the feces.

**Acetylation** — After absorption the sulfonamides are partially conjugated by the liver into acetylated forms which are therapeutically inactive and tend to be more toxic. This conjugation varies considerably with the different chemicals on the average in the following order: sulfapyridine 10 to 90 per cent, sulfathiazole 0 per cent, sulfanilamide 20 per cent, sulfadiazine 10 per cent, sulfaguanidine 5 per cent. This irregular and sometimes excessive conjugation has been an important factor against the use of sulfapyridine. This process does not occur with penicillin, streptomycin, etc. and therefore need not be discussed.

**Distribution** — Sulfonamides acquire an almost uniform distribution throughout the tissues and body fluids. There are however certain variations. Their concentration in tissues varies with the local vascular supply and is sometimes higher in exudates than in the blood. There are a few local variations. For instance, sulfathiazole is present in relatively low concentration in the spinal fluid and the erythrocytes but it is in average concentration in the meningeal tissues and its absence in the red cells may account for the rarity of hemolytic anemia. Also in chronically infected areas where vascularization is deficient the concentration of sulfonamides may be relatively low.

The distribution of penicillin and streptomycin is not so uniform as with the sulfonamides. They will pass with difficulty if at all into the serous cavities and spinal fluid. Therefore in lesions of these areas they should be injected directly. It has been mentioned that the sulfonamides are almost inactive in purulent collections whereas penicillin is not retarded. Therefore its direct injection after aspiration of the purulent exudate is indicated.

**Excretion** — All sulfonamides except sulfaguanidine are excreted mostly by the kidneys. Small amounts are found in the secretions of milk, sweat, saliva and tears. The urinary excretion is by filtration and there is a moderate degree of reabsorption by the tubules. Increased diuresis by any means increases the output while renal lesions impair it. A single dose of 4 gm. entirely disappears from the blood in twenty-four hours except in the case of

However in the treatment of infections, time may be the essence of success. Therefore the clinician may be on the horns of a dilemma. He may be faced with several difficulties, such as the imperative use of some possible specific agent immediately, the impossibility of obtaining a specimen of material from the locus of the infection, lack of immediate facilities for the identification of the infecting agent even if such material can be obtained, lack of facilities to determine whether the infecting agent even if identified is susceptible to chemotherapy or an antibiotic, and finally the practicability of specific therapy.

Although the ideal conditions for rational therapy are in the majority of cases lacking, this may not always be the case. It is impossible at the present time to place all patients who need such treatment in hospitals where the requisites mentioned above can be carried out. In fact not all hospitals by any means could fulfill these requirements even if all such patients were so admitted. This is no reason, however, that a rational procedure should not be carried out.

It is now fairly well established that neither the sulfonamides, penicillin nor streptomycin have an influence on the viruses known to be pathogenic to man with the possible exception of those of psittacosis and chorionmeningitis which are yet unproved. But there is increasing evidence that aureomycin is effective. Therefore it would be unrealistic to use them for the common cold, virus pneumonia, vaccinia, smallpox, rabies, encephalitis, etc. This does not exclude their use where there are secondary pyogenic infections as in smallpox where sulfadiazine and particularly penicillin are indicated and where from all indications streptomycin is the best of all. The same can be said for the common cold and atypical pneumonia which although not proved virus diseases have not been benefited by their use but a secondary infection with the streptococcus, staphylococcus, *Meddander's bacillus* or *H. influenzae*, which may be the determining factor is vulnerable to one of these agents. Chloromycetin is effective for gram negative infections.

When we turn to the rickettsial diseases we find a similar situation. There is no evidence that these agents have any influence on rickettsiae with the one exception that it has been established that penicillin inhibits the typhus rickettsia.

On the other hand many bacteria and fungi are inhibited by sulfonamides, penicillin, and streptomycin. An outline will be given of the organisms and the diseases which are susceptible to these agents and to what relative degree they are considered susceptible (Tables XXII to XXV). The same can be said of aureomycin. There is increasing evidence that it has an effect on both viruses and rickettsiae (Table XXV).

**Solubility and Absorption.**—Sulfanilamide is the only one of the sulfonamides which is readily soluble in water; all the others are insoluble except as salts, particularly the sodium combination. However they become quite soluble in the body cells and fluids and also in the intestinal tract and are nearly completely absorbed in two to four hours when taken by mouth. Sulfaguanidine is an exception. It is very slowly absorbed and seldom in ordinary doses reaches a level of over  $\frac{1}{2}$  mg. per cent in the blood. It therefore has an

TABLE XVI

SYMPTOM	SULFA DIAMIDE	SULFA ETHYLENE	SULFA THIAZOLE	SULFA PIAZINE	SULFA GUANIDINE
Aggranulocytosis	1 in 100	Rare	Less so	Less so	0
Anemia hemolytic	100	100	Very rare	Rare	0
Anemia secondary	20	20	Rare	Rare	0
Anuria	0	0.5	0.5	Rare	0
Conjunctivitis	0	0	100	0	0
Cyanosis	Common	Common	0	0	0
Dizziness	Common	Common	Rare	Rare	0
Erysipeloid	0	0	0	Rare	100
Fever	20	20	20	20	20
Hematuria	0	100	40	100	0
Hepatitis	Rare	Rare	Rare	0	0
Neutropenia	10	20	20	20	0
Rash	100	100	30	40	0
Rashes	20	20	40	100	20
Renal stone	0	0	0.5	1 rare	0.5
Vomiting	100	600	00	20	0

that tendency to recur with any subsequent course of treatment especially of the same drug, but occasionally on exhibition of one of the others. It is best to cease all sulfonamide therapy unless the risk is less than the benefit expected from their continuance in controlling an originally severe infection for which these drugs are known to be specific.

c. *Renal Stones*.—The deposits in the renal system are due to the acetyl fractions. Hematuria may be either microscopic or macroscopic. The most minor manifestation is a crystalluria. This may be a passing phase. On the other hand it may increase to extensive deposits in the renal tubules, large concretions in the pelvis and finally complete blockage of the ureters leading to hydronephrosis and anuria. This may occur with all sulfonamides except sulfadiazine and sulfaguanidine and of course calls for immediate stoppage of the drug. It is best combated by rendering the urine alkaline and promoting polyuria by the copious ingestion of fluids. At least 1200 cc should be taken each day. Surgical interference may be required.

d. *Hematological Changes*.—Hemolytic anemia of severe degree may develop with explosive suddenness. It is important therefore to keep a vigilant watch for its occurrence. This may occur during the early days of therapy and on occasion is wrongfully attributed to the infection. As agranulocytosis develops later in the course (after 12 days) it is well to check the white count every few days.

The toxic effects of the antibiotics are comparatively minor compared to those of the sulfonamides. Penicillin may cause skin rashes and occasionally a serum sickness like reaction. Since various salts of penicillin have been introduced such as Na, Li, NH<sub>4</sub>, Sr, Ca, Mg and K, the toxicity in experimental animals has been increased. It was concluded therefore that the toxicity of penicillin salts is primarily due to the cations used in their preparation.

Streptomycin exhibits very few toxic effects in man. There is sometimes a histamine like reaction characterized by nausea, headache, general malaise, skin rashes, arthralgia, vasodilation and fever. The second complication which is a serious one is the occurrence of a vestibular dysfunction and deaf

sulfadiazine which is slower. While both the free and acetylated forms are freely excreted by the kidneys, the latter may give rise to trouble through precipitation in the tubules, pelvis, and ureters to form casts in the first, stones in the second and sedimental blockage in the third. These conditions are enhanced by acid urine and oliguria and reduced by alkaline urine and polyuria. Therefore adequate intake of fluids is advantageous and excessive amounts may reduce this danger to a minimum but by excessive diuresis prevent adequate concentration in the blood and tissues.

Both penicillin and streptomycin are readily and harmlessly excreted through the kidneys. This is one of the principal difficulties in the maintenance of high blood levels even by repeated parenteral injections. There would appear to be considerable evidence to indicate that penicillin is excreted by the tubules. Therefore attempts have been made to reduce or block this by giving substances which are also excreted by this means. The first to be used was hippuric acid but this had serious gastrointestinal side effects. More recently other substances have been used with encouraging results. This is important as in cases where high blood concentration are required on account of the relative resistance of the organism satisfactory results can only be so obtained by such means or else by increasing enormously the amount of antibiotic given. Like procedures may be necessary for streptomycin.

It has been stated above that streptomycin is not readily absorbed by the bowel. The contrary may also be said of its excretion into the bowel. In other words, the intestinal wall is almost impervious to its passage.

**Toxic Effects**—One of the drawbacks of chemotherapy is the toxic reactions although these on the whole are not really of much consequence if kept in mind. These toxic results may be primary so to speak in persons who have not previously taken the drug. On the other hand similar effects more often develop as evidence of sensitization through previous administration. Although the latter occurs in about 2 to 5 per cent of cases it may not seem important until it be appreciated that these drugs are unfortunately taken and/or given promiscuously for all and sundry conditions whether indicated or not. It is most important that this should be appreciated as there is being built up a large number of people who may be sensitive and when a really serious illness occurs the drug may not be given with safety. In fact, one of the crimes of modern therapeutics is the promiscuous use of new drugs without reason or understanding. The principal toxic symptoms and their relative frequency are found in Table XXI.

It is true that the majority of these symptoms and signs are of little importance but there are four which should be taken seriously.

a *Fever*—This is of most importance as it may lead to a misunderstanding as to course of the disease. The fever of the infection except in complicated or unsuitable cases is usually normal in about 3 to 4 days. Therefore if there has been clinical improvement and the pyrexia continues it must be suspected as being due to the drug and its use should be discontinued. If this be the case the temperature will return to normal within 48 hours.

b *Skin rashes* are chiefly of importance as they may be a precursor of an exfoliative dermatitis. Rashes usually occur early in the therapy and have a

The dosages to attain these levels when administered by mouth, but with due allowance being given to individual variations in the rate of intestinal absorption are as follows:

Sulfanilamide—initial dose 3 to 4 gm followed by 1 gm every 4 hours day and night

Sulfapyridine—initial dose 3 to 4 gm followed by 1 gm every 4 hours day and night

Sulfathiazole—same as sulfapyridine

Sulfadiazine—initial dose 3 to 4 gm followed by 1 gm every 8 hours day and night

Sulfamerazine—initial dose 3 to 4 gm followed by 1 gm every 8 hours day and night

Sulfaguanidine—initial dose 3 to 10 gm followed by 3 to 4 gm every 4 hours day and night

Sulfasuxidine—10 to 15 gm followed by 3 gm every 4 hours day and night

It must be remembered that sulfadiazine and sulfamerazine are slowly excreted by the kidneys and that sulfaguanidine is slowly absorbed, in fact, the majority of the latter remains in the bowel contents and hence has an almost local action on intestinal flora and with diarrhea a great part is found in the stools.

Intravenous and subcutaneous therapy is usually confined to the initial dose unless it is impossible to give by mouth and for this the same amounts are employed in the form of the sodium salts but are repeated at longer intervals—6 to 8 hours for the first three days and 12 hours for sulfadiazine and sulfamerazine. Sulfaguanidine and sulfasuxidine are never given parenterally.

*Penicillin* is usually given intramuscularly. If in plain solution the intervals are every three hours day and night. This adds a considerable burden to the physician or nurse and is often objectionable to the patient. The intravenous routine is more exacting and distressing if the therapy has to be maintained over a prolonged period of time. Furthermore as the blood level must be maintained fairly constant throughout the twenty-four hours sleep is continually being disturbed. To avoid these objections and other minor ones the principle of administering it by intramuscular injection in a beeswax and peanut oil mixture as in histamine and desoxycorticosterone acetate therapy was explored. This was found to be successful in that the slow absorption permitted fairly constant blood levels (0.1 to 0.5 units per c.c.) to be maintained for six to eight hours. What might be termed adequate levels were attained when 40,000 to 60,000 O.U. were injected in 2.5 c.c. of this mixture. Such injections may be given three times a day or three hourly injections in aqueous solution may be given during the day and a beeswax and oil injection given at bedtime to insure a continuous period of sleep. Further advantage is to be found in conditions where short periods of penicillin action (12 hours) are sufficient as for example in acute gonorrhea 200,000 units in 2 c.c. of beeswax oil mixture will usually be successful. It is now usually agreed that the procaine salt of penicillin suspended in sesame oil containing 300,000 units of penicillin per c.c. is easily administered tolerated without discomfort has few toxic features and maintains fair plasma levels of the drug from sixteen

ness. The former is by far the more frequent. Whereas at first there was usually a residuum, with the reduction in dosage the frequency of vestibular impairment has been conspicuously less.

An increasing number of cases are being reported of what might be considered an *avitaminosis* when penicillin, streptomycin, sulfaguanidine, or even sulfadiazine have been given by mouth. The symptoms and signs are usually described as resembling those of nicotinamide or riboflavin deficiency and some have a more extensive suggestion of a pellagrous condition. In some an estimate of the daily urinary output of nicotinamide and riboflavin has shown them to be markedly deficient. All symptoms promptly disappeared on cessation of the drug and institution of vitamin therapy preferably by the parental route. The exact cause of these secondary reactions is not yet clear but it is suggested that they are due to a pronounced decrease in the intestinal flora. The stools can be rendered sterile by streptomycin and on occasion by sulfaguanidine. It could be surmised that in the cases associated with penicillin and sulfadiazine they were of those unusual groups in which these substances pass through the stomach unaltered as in penicillin and that in both the absorption is impaired. Further work is necessary, but these cases sound a note of warning.

The toxic effects of streptomycin are very few and up to the present consist of a variable degree of nausea and vomiting. Reduction in the dosage or temporary withdrawal of the drug is usually effective. The use of 0.5 ounce of aluminum hydroxide with each 100 mg. oral dose has been advocated.

**Method of Administration and Dosage.**—Oral administration is the method of choice for all the sulfonamides unless there is an immediate demand for a high blood level. If this be required sulfanilamide being highly soluble in water may be given subcutaneously in a 0.8 per cent solution in physiological saline. The other sulfonamides are best given intravenously as the sodium salts of a 5 per cent solution in distilled water. Topical applications are also used but on account of its solubility sulfanilamide gives by far the best results by this means.

The dosage depends upon the following several factors which it is well always to keep in mind: the type of organism, the acuteness of the process, the severity of the primary systemic reaction, the rate of absorption, renal function, and the state of hydration. Under such conditions each case must be considered individually as the habit of routine procedure is sure to lead to trouble and in fact is a frank acknowledgment of unreasoned practice. When possible the course of the therapy should be followed by daily estimation of the blood levels of which there is an optimum for each drug. (free)

	MG PER CENT
Sulfanilamide	10 to 1
Sulfapyridine	5 to 10
Sulfathiazole	5 to 10
Sulfadiazine	5 to 10
Sulfamerazine	5 to 10
Sulfaguanidine	1 to 3
Sulfasuxidine	1 to 3

The dosages to attain these levels when administered by mouth, but with due allowance being given to individual variations in the rate of intestinal absorption are as follows:

Sulfanilimide—initial dose 3 to 5 gm followed by 1 gm every 4 hours day and night

Sulfapyridine—initial dose 3 to 4 gm followed by 1 gm every 4 hours day and night

Sulfathiazole—same as sulfapyridine

Sulfadiazine—initial dose 3 to 4 gm followed by 1 gm every 6 hours day and night

Sulfamerazine—initial dose 3 to 4 gm followed by 1 gm every 6 hours day and night

Sulfaguanidine—initial dose 5 to 10 gm followed by 3 to 5 gm every 4 hours day and night

Sulfisoxazine—10 to 15 gm followed by 3 gm every 4 hours day and night

It must be remembered that sulfadiazine and sulfamerazine are slowly excreted by the kidneys and that sulfaguanidine is slowly absorbed; in fact the majority of the latter remains in the bowel contents and hence has an almost local action on intestinal flora and with diarrhea a great part is found in the stools.

Intravenous and subcutaneous therapy is usually confined to the initial dose unless it is impossible to give by mouth and for this the same amounts are employed in the form of the sodium salts but are repeated at longer intervals—6 to 8 hours for the first three days and 12 hours for sulfadiazine and sulfamerazine. Sulfaguanidine and sulfisoxazine are never given parenterally.

Penicillin is usually given intramuscularly. If in plain solution the intervals are every three hours day and night. This adds a considerable burden to the physician or nurse and is often objectionable to the patient. The intravenous routine is more exciting and distressing if the therapy has to be maintained over a prolonged period of time. Furthermore, the blood level must be maintained fairly constant throughout the twenty-four hours; sleep is continually being disturbed. To avoid these objections and other minor ones the principle of administering it by intramuscular injection in a beeswax and peanut oil mixture as in histamine and desoxycorticosterone acetate therapy was explored. This was found to be successful in that the slow absorption permitted fairly constant blood levels (0.1 to 0.5 units per c.c.) to be maintained for six to eight hours. What might be termed adequate levels were attained when 40,000 to 60,000 O.U. were injected in 2 c.c. of this mixture. Such injections may be given three times a day or three hourly injections in aqueous solution may be given during the day and a beeswax and oil injection given at bedtime to insure a continuous period of sleep. Further advantage is to be found in conditions where short periods of penicillin action (12 hours) are sufficient as for example in acute gonorrhea. 200,000 units in 2 c.c. of beeswax oil mixture will usually be successful. It is now usually agreed that the procaine salt of penicillin suspended in sesame oil containing 300,000 units of penicillin per c.c. is easily administered, tolerated without discomfort, has few toxic features and maintains fair plasma levels of the drug from sixteen

to sixty hours after injection. It would seem probable that this manner of administration will prove quite satisfactory for most infections when indicated. The consequent economy of nursing effort will be most welcome.

Penicillin given by mouth in tablets to be sucked is sometimes useful for local buccal and pharyngeal infections but many doubts are raised in this regard. The period when a concentration of any degree is maintained is fleeting and the influence is superficial. On the other hand, with improved pharmaceutical preparations the oral route for attaining adequate blood levels with certainty may be accomplished. Until this be the case the chances of error are too great for this method to be advocated for general purposes.

Inhalation or "aerosol" therapy for penicillin has given excellent results in selected cases of laryngeal and bronchial infections due to susceptible organisms. The penicillin is nebulized by a variety of means and inhaled at regular intervals.

It has been mentioned above that penicillin does not pass as readily as would be hoped through inflamed serous membranes or the meninges. Therefore intrapleural, intrapericardial, intraperitoneal and intrathecal administration of a solution of the sodium salt is often an important accessory to its parenteral use. This is important as contrast to sulfonamides, penicillin is active in purulent exudates.

The dosage of penicillin varies considerably in different infections. This variation is interpreted in two ways: first the daily amounts and second, the number of days it is to be continued. In general the daily dose amounts to from 160,000 to 480,000 units. This may be given in equally divided doses every three hours in two doses in beeswax and oil or as one dose, by the procaine salt in sesame intramuscularly once a day or by continuous intravenous or intramuscular drip. As far as the action of the penicillin is concerned the method is immaterial provided an adequate and fairly continuous blood level is maintained.

The duration of the therapy represents much greater variations which may range from a single dose in beeswax and oil or the procaine salt to the continuous therapy over weeks in subacute bacterial endocarditis. It may be laid down as a general rule that in acute infections treatment from a few days to a week is sufficient while in the subacute and more chronic cases this may extend to thirty or more days.

*Streptomycin* may be given after the same methods as used for penicillin. There are however several variations. In the first instance it can be readily and effectively given by mouth by which method a satisfactory blood level can be maintained. Furthermore the contents of the gastrointestinal tract are converted temporarily to a sterile state but a few days after its withdrawal the growth of organisms returns. On the other hand it has the drawback that when given by the intrathecal route it produces what appears to be a foreign body reaction. Bacteria as a rule appear to become resistant to streptomycin more readily than they do to penicillin. Therefore the initial dosage should be relatively large if the course is to be of short duration.

The dosage of streptomycin varies somewhat according to the method of administration. It must first be stated that it may be prescribed either as



units or by weight—1 000 units being equivalent to 1 mg. of pure streptomycin or 1 000 000 units equal to 1 gm. Experience is not yet sufficient to be at all dogmatic as to the exact amounts which are indicated in any specific infection. As with penicillin the sensitivity of the organism is an important determining factor as is also its virulence to man. The level in the blood should be about 30 mg. per cc. at the peak. The average amounts by different methods of administration are usually as follows:

Intravenous administration	1 to 2 gm. daily in 6 doses
Intramuscular administration	1 to 2 gm. daily in 6 doses
Oral administration	0.5 to 1 gm. daily in 4 doses
Aerosol administration	0.5 gm. daily
Intrathecal administration	0.5 gm. daily

Although streptomycin is rapidly excreted in the urine the blood level falls more slowly than does penicillin. Therefore the intervals between administrations may be longer. It has been stated that streptomycin is poorly absorbed by the intestinal tract. The same is true for the aerosol method. But by parenteral injections a high blood level may be maintained since it can be recovered from ascitic and pleural fluids, aqueous and vitreous humours, amniotic fluid and bile. Only traces can be found in the normal spinal fluid but in acute inflammation of the meninges levels as high as 25 mg. per cc. are reported. It is well therefore to determine this level if possible before intrathecal administration is used.

Streptomycin is usually given by mouth as on account of its high acidity there are difficulties for the parenteral routes. It can however be given intravenously by syringe in a 5 per cent solution in 20 cc. of distilled or in 500 cc. in a proportionately weaker dilution. A procaine solution has been used intramuscularly but is not advised with present preparations. The dosage of streptomycin by the oral route is 5 to 10 mg. per kilogram of body weight every 6 hours or 0.5 to 1 gm. for an ordinary adult.

**Indications for Therapy**—It may be simply stated as a law that chemotherapeutic or antibiotic agents are indicated when a pathogenic infection is due to an organism which is sensitive to any one or more of them. Their indiscriminate use without knowledge of the probable organism and their possible value before making every effort to obtain a culture of material as a source of this information is the worst form of shotgun therapy. It is true that apparently good results may occur but one of the greatest hazards in rational therapeutics is what appears to be coincidence which really rests upon the fact that most infections are self limited and specific therapy is often given at the height of the disease. This is one of the principal fallacies of the catch as catch can conclusions of clinical therapeutics where the failures are forgotten or not given their proper weight. On the other hand critical and analytical clinical observations have been the basis for therapeutic advances whether it were digitalis in congestive circulatory failure, quinine for malaria, mercury for syphilis, cowpox vaccination against smallpox, thyroid extract for myxedema or cretinism, cod liver oil or sunlight against rickets or citrus fruits for scurvy. In their use the deduction of cause and

effect was fairly simple and direct, but in most infections there are several variables which must always be taken into consideration. These are:

1. What is the infecting organism specific for the disease syndrome such as tularemia, typhoid fever, tuberculosis, rabies, syphilis, Rocky Mountain spotted fever, etc?

2. What is the organism responsible for a nonspecific infection such as pneumonia, bacterial endocarditis, meningitis, sinusitis, peritonitis, enterocolitis, pleurisy, etc?

3. Is the specific causative agent of the disease or nonspecific organism sensitive to chemotherapy or antibiotics?

4. How virulent is the causative agent to the human organism? It is well known that *Staphylococcus aureus* in systemic infections is much more virulent than when localized in a furuncle or carbuncle and a much greater hazard on the average than is the *Streptococcus hemolyticus* in all forms. Also the gonococcus is as a rule a more benign pathologic agent than is the meningococcus. Other examples might be given but these would seem sufficient.

5. Where is the infection located? Is it local or systemic? Is it best attacked by local, oral, intrapleural, intravenous, intramuscular or intra-thecal methods of administration?

TABLE XVII

SUSCEPTIBILITY OF LIVING ORGANISMS TO SULFADIAZINE AND SULFAGUANIDINE

HIGHLY SUSCEPTIBLE ORGANISMS		
Sulfadiazine		Sulfaguanidine
✓ meningitidis		✓ dysenteriae
Str hemolyticus		
✓ gonorrhoeae		
D pneumoniae		
MODERATELY SUSCEPTIBLE ORGANISMS TO SULFADIAZINE		
	A pneumoniae	
	B anthracis	
	Cl welchii	
	Cl septicum	
	H influenzae	
	Staph aureus	

TABLE XVIII

SUSCEPTIBILITY OF THE LIVING AGENTS OF DISEASE TO PENICILLIN

HIGHLY SUSCEPTIBLE ORGANISMS		
H anthracis	Cl tetani	Staph albus (most strains)
B subtilis	Cl tetanomorphum	Staph aureus (most strains)
Cl histolyticum	C diphtheriae	Str bovis
Cl novyi	Diphtheroid brevis (most strains)	Str equinus
Cl oedematis	D pneumoniae	Str pyogenes
Cl welchii	H ducreyi	Str hemolyticus (except group D)
Cl septicum	✓ atartralis	T pallidum
Cl sporogenes	✓ gonorrhoeae	I prowazekii (murine typhus)
Cl sordellii	✓ influenzae	
MODERATELY SUSCEPTIBLE ORGANISMS		
A bovis	Cl chaenocys	✓ minus
Anaerobic streptococci	Ery rhusiopathiae	Str faecalis
For novyi	Lept icterchaermonis aquae	Str lactis
Bar recurrentis	M lysodeikticus	Str nonhemolyticus
Cl bifementans	Ornithosis virus	Str salinarum
Cl botulinum	E ittaecosis virus	Str viridans

6. Should a short intensive course be given or will it require a prolonged course and how concentrated should blood levels be?

All of these questions must be analyzed and answered by the physician to himself. But there are certain criteria which may help him to arrive at a conclusion. These rest upon the relative susceptibility of the various organisms to the different sulfonamides and penicillin, streptomycin or aureomycin. These are listed in Tables XXII to XXV.

TABLE XXII  
SUSCEPTIBILITY OF THE LIVING AGENTS OF DISEASE TO STREPTOMYCIN

HIGHLY SUSCEPTIBLE ORGANISMS	
<i>I. aerogenes</i>	<i>H. influenzae</i>
<i>Br. abortus</i>	<i>H. pertussis</i>
<i>Er. suis</i>	<i>M. mallei</i>
<i>D. pneumoniae</i>	<i>N. gonorrhoeae</i>
<i>L. typhi</i>	<i>S. schottmuelleri</i>
<i>Er. murisaepticus</i>	<i>Str. hemolyticus</i>
MODERATELY SUSCEPTIBLE ORGANISMS	
<i>I. anthracis</i>	<i>Myc. tuberculosis hominis</i>
<i>H. mucoides</i>	<i>List. septicus</i>
<i>H. subtilis</i>	<i>List. tularensis</i>
<i>C. diphtheriae</i>	<i>S. paratyphosarum</i>
<i>Esch. coli</i>	<i>Staph. aureus</i>
<i>K. pneumoniae</i>	

TABLE XXIII  
SUSCEPTIBILITY OF LIVING ORGANISMS TO AUREOMYCIN

<i>E. typhosa</i>	<i>D. pneumoniae</i>	<i>Staph. aureus</i>
<i>Esch. coli</i>	<i>N. gonorrhoeae</i>	
<i>K. pneumoniae</i>	<i>N. meningitidis</i>	
<i>I. aerogenes</i>	<i>Er. melitensis</i>	
<i>H. influenzae</i>	<i>Br. abortus</i>	
<i>Str. typhosus</i>	<i>Er. suis</i>	

A. Yet the susceptibility of many organisms to aureomycin has not been determined accurately. However, it is the most antibiotic applicable to man which reveals evidence of being effective against rickettsiae and viruses. Tentative list includes those believed to be the causative agent in the following diseases: lymphogranuloma venereum, granuloma inguinale, psittacosis, viral pneumonia, trichinosis, murine epidemic and scrub typhus, Rocky Mountain spotted fever, South African tick bite fever, tick bite fever, North Queensland tick fever and seven strains of Q fever.

It will be seen from the above that certain pathogenic agents are susceptible to one or more of the sulfonamides and antibiotics, but this is relative. There has been a constant endeavor to arrive at a quantitative assessment of their relative values, and this has been solved after a rather empirical fashion. By this is meant that the variables in human disease cannot be always compared with a controlled experiment. In spite of this, much has been accomplished in the prevention and cure of disease.

**Prophylaxis**—It has now been accepted on somewhat disputed grounds that certain diseases can be mitigated or recurrences even prevented by the use of some of these agents.<sup>3</sup> The following may be considered.

**Rheumatic Fever**—The supposed increase of recrudescences of rheumatic fever parallel with the mounting prevalence of *Streptococcus hemolyticus* flora in the nasopharynx has led to the custom of giving sulfadiazine in minimal doses over a prolonged period (years) with the object of reducing this flora during vulnerable periods (see Rheumatic Fever page 67). The validity

of this procedure may be doubted, but the fact remains that we are so helpless in the face of this disease that any straw is worth grasping. The only hazard is in the probability that the streptococcus if present will become resistant to one or another of these agents. This may be unavoidable, but is not so serious as the possibility that the host may become sensitive to the drug.

*Streptococcus Sore Throat*—A somewhat similar result has been obtained in the handling of this condition in groups of recruits in schools etc. where young people or children live in close contact. The use of 0.5 gm. of sulfadiazine twice a day has produced a conspicuous reduction of cases. This is primarily applicable to air borne infections and not to milk which is best handled by detection of a carrier among the milk handlers or in the kitchen and pasteurization of the milk.

*Scarlet Fever*—The same method may be employed for contacts with scarlet fever, but it should not be advocated for the population in general both on account of the risk of toxic reactions and the production of sulfonamide resistant strains.

*Gonorrhea*—It has now become an accepted custom for prostitutes and their habitual consorts to take sulfonamides (sulfadiazine) or penicillin by mouth as a protective against gonorrhea. Their value to the consorts is dubious as for the prostitutes it is even more so as it has been demonstrated that in time they may and often do harbor a resistant strain of this organism which although attenuated to them is virulent to another host.

*Parturition*—There are on occasion reasons to believe that a gonorrheal infection may be reactivated or the probability of a primary pyogenic infection initiated which might lead to a septicemia or even a bacteremia. It is therefore proper to give either sulfadiazine or penicillin in proper amounts to forestall such an infection. The pyogenic organism is usually the streptococcus. If another bacterium is subsequently isolated as the causative factor the most efficient drug should be employed.

*Smallpox*—The use of sulfonamides and the antibiotics to control the staphylococcal infection of the skin lesions of this disease and varicella has given most encouraging results. They should be started as soon as the vesicles appear and be continued until the crusts have fully desiccated and are spontaneously dropping off.

*Preoperative*—It has become a custom with many surgeons to give a short course of penicillin before all operations and to continue for several days afterwards. The rationale is to prevent secondary infections. This would hardly seem necessary unless there were a fear of a break in the aseptic technique. Such procedures often give a sense of false security and such breaks are then more likely to happen.

On the other hand there are some operations which require through their very nature that healthy tissues may be soiled by infected material or that there is a great hazard that this might occur. Therefore the agent which is effective against the organism which is most likely to be the principal pathogen should be used after a prophylactic manner.

Operations upon the large bowel and rectum are notoriously hazardous as to secondary infections. The sulfonamides and penicillin were indifferently

useful in combating these conditions but streptomycin has been conspicuously successful. It should be given by mouth (1 to 2 gm per day) for 3 to 4 days before the operation. This will practically suppress bacterial growth in the feces. Immediately following the operation it may be given intravenously or intramuscularly in the same amounts for a few days. It has been pointed out above that there is little or no transfer of streptomycin through the bowel in either direction therefore it should be given in a proper sequence.

**Leucopenia**—In a number of acute infections, leucopenia is characteristic. In most of these secondary infections with pyogenic organisms are fairly common particularly as furuncles, carbuncles, impetigo or pneumonia. The following is a list of these diseases: typhoid fever, typhus, influenza, Rocky Mountain spotted fever, measles, malarial virus pneumonia, etc. It is therefore proper to use the proper drug against the pyogenic agent which is chiefly the *Staphylococcus aureus* in spite of the fact that it is of no value in the original disease.

There are conditions which are not primarily infections in which these drugs are of great value such as in granulocytic anemia and in the leucemic phase of leukemia. The organisms which are most commonly accountable for the anemia in these diseases are the staphylococcus and the streptococcus. Therefore penicillin in full doses (400,000 to 600,000 units per day) should be given with complete appreciation that it is used for prophylaxis of infection and not for cure of the original condition.

The prophylactic use of these agents under specific conditions does not imply that they should be used as a routine for the prevention of for instance pneumonia, erysipelas, scarlet fever, meningococcus meningitis, etc. Such a program would undoubtedly do great harm but unfortunately it is done by the busy far too often.

**Curative Therapy**—In addition to the prophylactic use of these agents there will now be considered their curative value and range of use. It should be a fundamental rule that the agent of choice should be so administered as to reach the locus of infection in the greatest concentration. This is usually attained through the blood stream by intravenous or intramuscular injections but there are circumstances which would indicate that additional methods should also be used. These may be summarized as follows:

1 In pharyngeal, laryngeal, bronchial and pulmonary lesions the parenteral method should be supplemented by the aerosol method for penicillin. In fact the latter may be used exclusively in chronic lesions.

2 In enterocolonic lesions streptomycin when indicated for a specific organism should be given both by mouth and parenterally. The latter method is always indicated during the acute stages and the former in the more chronic conditions but both methods have their place under particular circumstances. Vigilance should always be exercised to detect the remote but real secondary results as mentioned above (see page 1431). Aureomycin and streptomycin have also given encouraging results when used in typhoid fever and gram negative bacillary lesions in the urinary tract. They also would appear to be effective in undulant fever.

■ When the serous cavities the joints, the paranasal sinuses the middle ear, and the meningeal space are involved, direct injection of penicillin or streptomycin when indicated should be employed

4 The topical application of sulfonamide, penicillin, and more rarely streptomycin or aureomycin may be used in cutaneous lesions and other accessible local lesions. But these conditions usually, but not always, require also parenteral therapy

Although through the previous text many statements have been made as to when these agents are indicated it is now considered proper to summarize these for easy reference (see Table XXVI). It must be appreciated however, that this summary is not absolute as with experience their relative value and further extension or contraindication leaves this question in a constant state of flux.

TABLE XXVI

<i>Pneumococcus</i>	
Penicillin—	320 000 O.U. per day intramuscularly and continued until temperature is normal for five days
Sulfadiazine—	6 gm per day by mouth until the temperature is normal for five days. An initial dose of 4 gm should be given intravenously in severe cases
<i>Friedlander Bacillus</i>	
Streptomycin—	2 gm per day intramuscularly until the temperature is normal for five days
Sulfadiazine—	as given for pneumococcus infections
<i>Staphylococcus</i>	
The agents of choice are the same as for the pneumococcus and after the same dosage and method	
<i>Streptococcus</i>	
The agents of choice are the same as for the pneumococcus	
<i>Meningococcus</i>	
Sulfadiazine—	6 gm per day by mouth until the temperature is normal for one week and the spinal fluid is sterile
Penicillin—	15 000 O.U. intrathecally and 240 000 O.U. intramuscularly until the temperature is normal for one day
<i>Gonococcus</i>	
The agents of choice are the same as for the meningococcus and should be used in the same amounts in severe cases but shorter period as usually sufficient in early local infections	
<i>II Influenza</i>	
Sulfadiazine—	6 gm per day until the temperature is normal for five days
Streptomycin—	1 gm per day intramuscularly until the temperature is normal for five days. Streptomycin is only indicated in severe pneumonia meningitis endocarditis bacteremia etc. due to this organism

It will be noted from Table XXVI that aureomycin may be substituted on occasion for either sulfonamides or penicillin or streptomycin. But it would appear that it has a unique influence upon rickettsial and viral infections. In addition to those already mentioned it has been found to be efficacious in the viral infections of the eye.

These are examples of the dosage and methods of therapy against a few of the common organisms which are sensitive to these agents. It must be appreciated that all infections are not of the same virulence and may affect different tissues. A good example is in the case of the *Streptococcus viridans*. This is usually an organism of mild pathogenicity but when it is the cause of subacute bacterial endocarditis although the course was long and often com-

paratively mild the end result was usually fatal. But penicillin used in full doses is above and continued for at least 25 days irrespective of the absence of symptoms usually brings about a complete cure. It must be ascertained however, that the strain of the organism is sensitive and does not become resistant and that a sufficiently adequate blood level is maintained.

At the present time the value of streptomycin in the treatment of tuberculosis is in the stage of investigation. There is no doubt that it is an effective agent against the *Mycobacterium tuberculosis* in experimental animals but it is difficult to translate these into practice in man where the variety of the anatomical changes are so diverse. It would seem logical that it would be most efficacious in the early exudative stages whether in children or adults. It would be immaterial whether such a lesion were in the pharynx, larynx, bronchus, lung, parenchyma, etc. Military tuberculosis would seem to offer a good hope of a satisfactory result. When tuberculous meningitis is present however the results have not been as satisfactory as could be wished. There is little doubt that life is prolonged but the final result seems to be partly influenced by a foreign body reaction in the meninges which so often occurs. There is one important fact that must always be borne in mind. This is the case with which the *Mycobacterium tuberculosis* requires a resistance to the antibiotic. There appears to be a growing tendency to employ streptomycin in all and sundry types of tuberculous infection. This is to be condemned. It may be stated according to our present knowledge that it should not be used under the following conditions: (1) Early minimal parenchymal lesions which would be expected to respond favorably to a rest cure with or without collapse therapy. (2) Advanced fibro-vegetative lesions (except in the below). (3) It should not be used in ambulant cases to the exclusion of a rest cure and/or collapse therapy. On the other hand its use is indicated in the following: (1) Military tuberculosis. (2) An exudative parenchymal lesion which is not responding favorably to rest cure with or without indicated collapse either on account of local spread or continuing severe systemic reaction. (3) Acute tuberculous pneumonia lesions. (4) Tuberculous lesions which militate against a proper cure such as tuberculous pharyngitis, laryngitis or tracheitis if the first is a serious hazard for nutrition and the last two through severe coughing, pyrexias rob the patient of rest. (5) Tuberculous bronchitis without evidence of fibrotic stenosis or a distal parenchymal lesion for which future surgical interference would be indicated. (6) In preparation for major surgical operations such as thoracoplasty and particularly lobectomy or pneumectomy and also following such operations to prevent possible local or contralateral spread.

It must be emphasized that the use of streptomycin is at present in an exploratory stage. Future experience may and probably will modify our present concepts but for the present it must be appreciated that there is much still to be learned from critical and well controlled observations.

Aureomycin is one of the more recent antibiotics which has become available for use in human disease. It holds great promise as a valuable agent against certain rickettsiae and viruses as outlined in the footnote to Table XXV. The exact manner of its action in these infections is not at present

known, but it is hoped that in the near future this will be clarified as this may unlock an entirely new field of intracellular pharmacology. It would seem that it acts as a bacteriostatic agent to the organisms in bacterial diseases, many of which are also vulnerable to the sulfonamides, penicillin and streptomycin, and also it is antagonistic to certain gram-negative organisms which have so far been resistant to the agents. But this may not necessarily be so in the case of the rickettsiae and viruses.

The impetus given to the exploration for new antibiotics is opening up a constantly broadening field in human therapeutics. Many antibiotics have been discovered but relatively few are applicable to man. There are some, such as chloromycetin which hold great promise but it is hoped that the use of all will be properly evaluated before our enthusiasm runs away with knowledge and common sense.



## CHAPTER XVI

### DISEASES DUE TO ALLERGY

#### INTRODUCTION

The role of allergy in the causation of anatomical and physiological disturbances in the body has come into prominence during the last generation. The rapid advances made in this conception of the etiology of disease have led to considerable confusion in the definition or interpretation of a number of terms which it would be well to clarify before we proceed further.

*Immunity* is that state of individual cells or the organism as a whole which protects them from the deleterious action of bacteria or foreign proteins or other chemicals.

*Anaphylaxis* was applied in 1893 by Richet to indicate a state in which there was increased susceptibility, increased sensitiveness or hypersusceptibility to similar substances in contrast to immunity.

*Allergy* should be defined as that state where there is an altered reaction which may be either more rapid or more intense to these substances. In many instances it is synonymous with the older, more general and less definite term of *idiosyncrasy*. It is now usually accepted that *allergy* is inclusive of or synonymous with hypersensitiveness, sensitization, *idiosyncrasy*, anaphylaxis and atopy. As far as is known, decreased susceptibility or immunity to bacteria, foreign proteins or other chemicals does not produce any disease pattern. There is little doubt that confusion still exists in the interpretation of clinical anaphylaxis and/or allergy. Before proceeding further it would be well to deal with what is commonly known as serum disease or serum sickness.

#### SERUM DISEASE OR SERUM SICKNESS

Serum sickness is used to describe a series of phenomena which sooner or later develop in individuals who are sensitive to the serum employed. The response may be either immediate or delayed. It would probably be better if the usage of these terms were restricted to the delayed or late phenomena which sometimes go by the term normal serum disease. The symptoms are supposed to be produced by the foreign protein in the serum and not by any specific antitoxic, opsonic, lytic or agglutinating properties which the serum may have. Therefore there has been a continuous attempt made to render all protective sera as free of proteins as possible and as this cannot be completely accomplished the protective bodies are concentrated in a solution which contains small protein fractions and can be administered in small amounts. The majority of protective sera are manufactured by immunizing horses. Therefore the most common forms of serum sickness result from the injection of horse serum and this will be taken as the example to illustrate this condition.

**Incidence**—There are considerable differences in individual susceptibility to horse serum and about 10 per cent of people can tolerate large amounts. This is probably due to their being very slightly susceptible rather than completely immune. North American Indians and Negroes are less susceptible than the white race. There is every reason to expect that a person who has had serum more than fourteen days previously will be more or less susceptible, but there are many who have never had such injections but may be equally so. Therefore it is always wise, before serum is given, to determine the susceptibility of the individual. This can be done either by skin reactions or by the intravenous injection of minute quantities.

**Symptoms**—The incubation period is modified by whether or not the patient has had serum previously. If it be the first injection, symptoms usually appear in from six to twelve days and rarely after two to three weeks. If he has had serum previously, this period may be considerably shortened. The first sign, if sought for, is a general adenopathy and occasionally a palpable spleen. These may precede the appearance of skin rashes by several days. The latter, however, are the first symptoms of which the patient complains. The eruption usually begins as an urticaria in irregular wheals. This is soon followed by localized or diffuse erythema and there is considerable pruritus. The rash is sometimes morbilliform or scarlatiniform and rarely purpuric. The distribution may be either patchy or diffuse. Pyrexia occurs in about 30 per cent of the cases as does also edema. The former may range from 100° to 104° F. The latter may vary considerably and is most prominent in the face, particularly about the eyes. Its general distribution is irregular not only in degree but also in extent and may even simulate the edema of nephritis. With it there is a definite chloride and water retention with albuminuria and casts. In rare instances nitrogen retention has been reported. Another common occurrence is arthritis. The incidence of this varies from 20 to 60 per cent of the reported series of cases. There are usually pain, tenderness and limitation of movement of one or more joints. In a small number of these cases there are also swelling, redness, tenderness and signs of exudate which is of an inflammatory nature containing many cells, up to 25 000 or 30 000 per cubic millimeter, principally granulocytes although mononuclear cells are also present. The arthritis develops several days after the eruption. Occasionally edema and hyperemia of the retina and optic discs have been reported as have also optic neuritis and signs of spinal fluid involvement as indicated by increased number of cells and globulin in the spinal fluid.

Other signs and symptoms of less conspicuous frequency are vomiting, diarrhea, abdominal cramps and headache which is often intense when associated with changes in the spinal fluid and there may also be profound lethargy. The changes in the leucocytes vary with time. There may be a definite eosinophilia and an immediate leucopenia especially in children followed by a leucocytosis or the leucocytes may return to normal. In the European literature there have been a number of cases reported of polyneuritis developing later in the course of the illness. Recurrences of the rashes are sometimes observed, and these are most apt to be morbilliform.

**Pathological Anatomy**—There has not been much opportunity to investigate the anatomical changes in man. The cause of these symptoms is attributed to the presence of precipitins or other antibodies. They may be present in the cells or free in the plasma and by about the seventh to the ninth day, or thereafter, are present in sufficient concentration to give a reaction with the antigen if it be injected. The violence of this reaction depends upon three factors—concentration of the antibodies, the amounts of the antigen injected, and the route of the injections the four of which give intensities of reaction in the following ascending order—intradermal, subcutaneous, intramuscular and intravenous. It will be seen, therefore, that the concentration of the antigen in the plasma at any one instant plays an important role in the violence of the reaction. The exact manner whereby these symptoms are produced has been the subject of much discussion and experiment. There is not necessarily any direct relationship between the amounts of antibody in the plasma and the severity of the systemic reaction. It would appear more probable that the higher the intracellular concentration of the antibody when the antigen is injected the more severe will be the reaction as if this combination releases some substance from the cells which by its own action produces these symptoms. It has been suggested that this substance may be histamine or an allied body (see below).

**Diagnosis**—The diagnosis of serum sickness does not offer any particular difficulty provided there is a history of the administration of serum a short time previously. It may be confused with measles, scarlet fever, meningitis and sometimes with nephritis. The pruritus is of great importance in differentiating the skin rashes from specific exanthemata, particularly when the administration of epinephrin gives temporary relief.

**Course**—The disease usually lasts from a few hours to a week and as already mentioned relapses may occur. Recovery is the rule.

**Treatment**—The best treatment is prevention. This is not always possible in its entirety. When it is proposed to give a serum for therapeutic reasons it is well to determine if the patient is sensitive and to what degree. This can be done by the intradermal injection of minute but graded amounts into the skin. If the patient is sensitive a small amount of the serum is injected subcutaneously with the hope that desensitization may be accomplished with a minimal reaction. It is true that this may not be successful but when a serum reaction should be avoided it may be tried. The active treatment is symptomatic (see below). histamine, benadryl, pyribenzamine and other antihistamine drugs have all been used with equivocal results. The pruritus may be temporarily relieved by calamine lotion, sodium bicarbonate baths or injections of epinephrine. There are indications that the use of salicylates before the eruption appears may prevent or mitigate it and this is claimed to be due to the action of these drugs in preventing or limiting the production of precipitins.

### Serum Shock

**Synonym**—Anaphylactic shock, serum accidents

**Definition**—An explosive and frequently fatal reaction which may immediately follow the intravenous administration of horse serum.

**Etiology**—This condition occurs particularly in those who through their proximity to horses have become subject to asthma or paroxysmal rhinitis, and also in persons who have had a previous injection of horse serum. In the former the symptoms are as a rule much more severe than in the latter. These accidents or reactions are considered to be anaphylactic in the true sense. The similarity to experimental anaphylactic shock is particularly striking in those who have received, weeks, months or even years previously, an injection of horse serum when the symptoms are precipitated by a subsequent injection. The relation of serum shock to serum sickness would seem to be one of degree rather than of a different order. The antigen must be injected intravenously to produce serum shock in its full intensity. It is true that the injection of large amounts of antigen by the subcutaneous or intramuscular routes may produce immediate reactions, but these are usually comparatively mild.

**Symptoms**—The onset is immediate, often occurring before the needle has been withdrawn from the vein. There is first a feeling of intense apprehension with almost coincident urticaria edema of the face and extremities and sometimes of the whole body. There are also sneezing, a burning sensation in the throat, choking, cough, frothy sputum, and respiratory obstruction causing severe dyspnea and cyanosis. Signs of collapse such as dilatation of the pupils, rapid, thready pulse, falling blood pressure, mental confusion, and frequently convulsions rapidly develop. Pyrexia may follow. There is an almost immediate disappearance of the leucocytes from the circulating blood and other changes in the blood which will be mentioned below in the discussion of traumatic shock. Death sometimes is almost instantaneous or symptoms may be delayed for some minutes even to half an hour. The cases that are most likely to be fatal are those giving a history of horse asthma or rhinitis. When death does not occur the symptoms of serum disease may develop shortly or after a few days.

**Treatment—Prophylaxis**—The prevention of these untoward accidents depends upon the recognition of those patients who are hypersensitive and their desensitization. Therefore all patients to whom serum is to be given particularly intravenously should be questioned as to familial or personal history of other allergic phenomena such as hay fever asthma or urticaria and also as to whether the patient has had previous inoculations of protective sera. If any of these points are elicited the person should be tested by an intracutaneous injection of 0.1 cc. of one in ten solution of horse serum. If there is a positive local reaction it will then be necessary to carry out desensitization. If the skin reaction is strongly positive the first desensitizing dose of 0.025 cc. of horse serum should be given subcutaneously and at half hourly intervals it is doubled until 1 cc. is given. If no severe reaction has occurred the first intravenous dose of 0.1 cc. of serum in 5 cc. of saline is then administered. Every twenty minutes this amount is doubled until full doses are given. The specific protective serum to be administered may be employed for this intravenous desensitization. If the serum is to be given intraspinally, the same precautions for desensitization must be carried out. If the intracutaneous reaction is slight the procedure outlined above may be hastened by giving larger desensitizing doses.

On all occasions when intravenous protective sera are to be given, a hypodermic syringe containing 1 cc of epinephrin should be at hand for immediate use in case of the slightest suggestion of a reaction. If it be severe, several injections at intervals of a few minutes should be given. In fact 2 cc may be given at one dose in urgent cases.

## ALLERGY

With serum sickness as a background, it now seems proper to discuss the relations of what are generally called clinical allergic reactions to anaphylaxis. Are they identical, are they related, or are they quite independent phenomena? An exploration into these matters will soon lead us into a maze of truths, half-truths and speculations, but there are certain points which should be appreciated. In the first place the symptomatology of serum sickness and combinations of specific clinical allergic reactions have a striking similarity and in addition there is a common feature in both conditions. The most important manifestations of the allergic reactions are found in the sensitiveness of the skin and mucous membranes to this specific form of stimulation and also a tendency to produce contraction of smooth muscle as found in the bronchial tree and gastrointestinal tract. These reactions occur both in individuals who have been artificially sensitized to horse serum and in those who develop allergic phenomena such as asthma, but in the latter precipitins and smooth muscle sensitizing bodies cannot be demonstrated. Therefore it is only the outward similarity of these phenomena which appear analogous. It would be much easier if we could accept the conclusion that the two processes are identical, but whereas serum sickness may be produced by any foreign protein, it cannot be accomplished by focal or strictly chemical means of a non-protein nature. Therefore the identity of these two reactions must still be considered not proved.

The allergic patterns as they occur in man have certain common features although these may be modified in degree by the tissues in which they occur. They may be of the following nature: (1) edematous (2) hyperemic (3) hypersecretory (4) exudative (5) hemorrhagic. This general order of reactions occurs in part or in the whole in the skin, mucous membrane of the nose, nasopharynx and accessory sinuses, the larynx, trachea and bronchi or the mucous membrane of the gastrointestinal tract. There is little proof that it may occur in other viscera except probably in paroxysmal hemoglobinuria. It has been suggested that allergy plays a part in certain progressive visceral lesions such as cirrhosis of the liver, chronic nephritis and rheumatic heart disease. At present these latter are in the realm of being not proved although there are a number of points that make the idea intriguing. The association of certain cases of migraine, headache, focal and general epilepsy, vasomotor disturbances and the presence in some of these of known allergic phenomena has opened up a field of investigation which is well worth pursuing and may be taken as suggestive that visceral allergy can occur. The differences in the tissue responses, as for instance in the type of secretion in bronchial asthma and in paroxysmal rhinorrhea, are not dependent upon any modification of the fundamental reaction but rather are due to the essential differences of the

secretory product of these two mucous membranes. The more intense the allergic response the more likely is it to approach an exudative and hemorrhagic lesion. The great majority of allergic manifestations are usually confined to the first three, namely, edema, hyperemia, and hypersecretion.

Before proceeding further it would be well to review some of the general causes that may produce this condition. It must be remembered that the specific serum sickness is due to proteins alone, but this does not apply to clinical allergy in general. The forces which differ most from pure proteins are physical agents such as heat, cold, light, and cutaneous friction. Between these two groups there are a great number of substances such as foods including fish, meat, vegetables, fruits, and grains, epidermal products such as hair, dandruff, and feathers, the pollens of plants, trees and grasses, bacteria of all kinds, and finally drugs such as aspirin, quinine, potassium iodide, mustard, opium, morphia, certain sulfonamides, and a host of others of many different orders.

There is no proof that the so called sensitiveness of man to this great variety of stimuli is due to specific precipitins or other detectable bodies. The common factor in them all is their capacity under special individual conditions to produce the reactions outlined above and stimulate smooth muscle. We have used "stimuli" in the sense that all contacts with our external environment act as such. Reactions to stimulation which are usual in the majority are considered as normal, but if the same stimulation produces an unusual effect it is considered abnormal. This difference is not inherent in the stimulus but in the reaction of the organism to it. It is true that the intensity or amount of the stimulus may modify the reaction in the individual, but this is a quantitative response and in average individuals would be more or less of the same order as for instance a slight degree of heat applied to the skin would produce a mild and fleeting erythema while a similar stimulus of sufficiently great intensity would lead to tissue necrosis. This establishes the difference between a beneficent stimulation and a tissue insult. Similarly  $\frac{1}{4}$  gram of morphia given hypodermically produces what we call a physiological or pharmacological effect of the drug but 14 grains similarly administered would be poisonous and produce a toxic effect. Therefore in the interpretation of allergic reactions we are taking into consideration not so much the intensity or character of the stimulation but whether the stimulated person responds in an abnormal fashion or in a manner that would indicate that a mild or physiological stimulus produces an insult or toxic effect. In seeking some explanation of this sensitiveness to external stimuli a search naturally has been made for some substance which being present normally in the system might be released in large quantities or to which an individual might be sensitive even in normal amounts. A substance also which when administered in large or toxic amounts would induce phenomena similar to those of serum sickness, serum shock or the less specific allergic reactions.

### Detection of Allergy

When a patient presents symptoms which would suggest an allergic reaction (such as are presently to be described) the family history should be

thoroughly inquired into for any similar familial tendencies. Also there should be a close inquiry into any conditions or associations with which these reactions may be related. A host of leads must be followed, such as indisposition or dyspepsia following certain foods, or occurrence of symptoms when near animals, such as cats, dogs, horses; household articles such as pillows or bedding, the period of the day or year when the attacks are most common, exposure to cold, heat, light or friction; the presence of flowers in the house; the taking of drugs, particularly analgesics and hypnotics. Often the detective work is comparatively simple, as for instance a history of a person who always has an attack of rhinorrhea or asthma at three o'clock in the morning would naturally suggest that it is caused by or at least associated with, the bedding. It might be feather pillows, woolen blankets or a horsehair mattress. Some may not be able to abide the presence of a cat; others are prevented from eating buckwheat, honey, shellfish, strawberries or pork. Again there are those who claim they cannot take a cold bath, as immediately afterward they are afflicted with hives, urticaria, or violent attacks of sneezing or dyspnea, and even syncope. The presence of any focus of infection, particularly in the respiratory passages, should be carefully sought for. Out of such a searching history definite leads frequently develop. The next step is to determine whether the individual is skin sensitive to any of these conditions or substances. This is done by either the scratch method, intradermal method or patch test.

**Scratch Method**—The superficial layers of the skin over a tiny area are removed by a needle or other sharp instrument. Serum is not to be drawn and a small amount of the allergen, either dry or in solution, is then applied. This is repeated with as many substances as have been suggested by the history.

In the intradermal method a small amount (0.01 to 0.02 cc.) of a sterile solution of the allergen is injected into, but not under the skin.

The patch test is particularly applicable for those substances which produce a so-called dermatitis such as poison ivy, nettles, talcum powder, dust, ing powder, personal clothing (silk, cotton, linen or wool, etc.). A small amount of the suspected material or an extract thereof upon a piece of blotting paper is applied to the skin and held in place by a piece of adhesive plaster. A reaction similar to the dermatitis will be produced if the patient is sensitive.

The reactions to all these methods may be either immediate or delayed. The former develops within five or ten minutes and assumes the form of a wheal which may be itchy. The reason for this immediate reaction is not known but it strongly resembles the local reactions due to histamine. However, it has been found in these cases that a circulating skin sensitizing 'antibody' can be demonstrated in the serum by passive transfer. The delayed reaction may occur after some hours or even several days and would appear to be similar to the response in serum sickness.

Ophthalmic tests have been advocated from time to time but are not without danger. They are done by introducing into the conjunctival sac a small amount of solution of the suspected allergen. In about five minutes there are conjunctival redness, swelling, itchiness and lachrimation.

## Urticaria

**Synonym**—Angioneurotic edema

**Definition**—Urticaria is a term applied to a superficial localized edematous condition of the skin which is intensely itchy, while angioneurotic edema is reserved for deeper or subcutaneous areas. In both conditions there are redness of the skin, and an intense pruritis. They are commonly known as "hives." For many years it was considered a neurosis, but now there is no doubt that it is a definite allergic reaction. These swellings may occur on the mucous membrane of the mouth, pharynx, larynx, and have been detected in the esophagus and the mucous membrane of the gastrointestinal tract.



10—Urticaria (Courtesy of Dr Otto Leslie Castle: From Sutton and Sutton: Diseases of the Skin)

They are produced by a vast variety of substances such as feathers, hair, dusting powders, house dust, etc., but probably the most important are foods such as milk, eggs, peas, beans, shellfish, and also many drugs. The list is almost interminable. Such persons are frequently sensitive to many substances. The skin tests are not satisfactory in these cases, and to detect the cause one must frequently resort to a process of elimination, or in other words, trial and error.

**Treatment**—The immediate treatment consists of the application of soothing lotions, and a hypodermic injection of 0.5 cc of epinephrin. This usually brings about some relief, but the condition soon returns unless the primary cause can be eliminated. It may be present constantly if the cause is constant, or intermittent if the stimulus is present on relatively rare occasions, as when shellfish or strawberries are eaten, or when aspirin, quinine, or the coal tar products are taken as analgesics or hypnotics. Specific treatment is the same as for hay fever.



## Hay Fever

**Synonyms**—Allergic coryza, rose fever, paroxysmal rhinorrhea, paroxysmal rhinitis, vasomotor rhinitis, and pollinosis

**Definition.**—This is an allergic condition of the mucous membrane of the nose, conjunctiva, and upper respiratory tract. It is usually due to the inhalation of pollens, but may be caused by emanations from other substances and by foods.

**Symptoms**—When due to pollens there is usually a definite seasonal incidence. This will vary according to the latitude at which the individual is living. In the spring of the year it is frequently associated with the pollen of trees such as the alder, hickory, oak, ash, elm, and poplar, while in the summer it is most frequently due to the pollen of flowers and grasses such as the rose and hay. Toward the autumn many cases are due to the pollen from ragweed and buckwheat. It may be present intermittently throughout the whole year if the flower, the pollen to which the individual is sensitive is brought into the house.

Local infections of the accessory sinuses may also produce a similar reaction and under these conditions the seasonal periodicity will not be conspicuous but the reaction will be intermittent, occurring throughout the year. There is a swelling of the mucous membrane with hyperemia and hypersecretion and these vary greatly in intensity from a mild coryza to an intense rhinorrhea and lachrimation. The mucous secretions contain many eosinophiles and there is often an eosinophilia. There is a sense of burning and paroxysms of sneezing are most distressing. Nasal obstruction occurs, due to the swelling of the mucous membrane. As in all forms of allergy, hay fever may not occur alone but may be associated with asthma, urticaria and eczema. These conditions may appear in sequence or any of them may be present at the same time.

**Diagnosis**—The diagnosis of hay fever as such offers little difficulty but the cause may be extremely elusive. It is only by continuing to seek for this, and removing or avoiding it that an eventual cure can be hoped for. It would serve no useful purpose to enumerate the possible causative agents.

**Course**—The course usually follows a seasonal repetition unless a complete diagnosis is made and the cause is removed or the individual is desensitized. Many cases can be relieved and a permanent cure can be effected in a certain number.

**Treatment**—Although the cause may not be found often by repeated trials patients find a district in which they are completely free of symptoms but one patient who finds his freedom in the mountains may not at the sea shore and in another it might be the reverse. Therefore each victim must try to find his own salvation. Certain districts are supposed to be comparatively free of hay fever due to ragweed and goldenrod such as northern Maine, New Brunswick, Nova Scotia and the Province of Quebec north of the St. Lawrence also the White Mountains and southern California but it is interesting to note that ragweed is not necessarily absent in these localities.

**Specific Treatment**—If the proper pollen can be determined, vaccination against the cause is sometimes successful. This is accomplished by giving minimal injections of the pollen extract in increasing amounts, beginning some ten to twelve weeks before the expected onset of the disease. The amount to be given will depend upon the sensitiveness of the individual. The greater this is, the smaller should be the initial injections. One should not be too optimistic as to the results. Asthma due to pollen is usually greatly benefited, but for hay fever the results are not as good, and at best are temporary after one course of treatment. If the patient should seek relief immediately before an attack is expected or during one, it is well worth while to give a series of inoculations but these should be of very small amounts. The best method of specific treatment is to continue the inoculations throughout the year giving an injection every two to three weeks and with the maximal amount that the patient can tolerate without producing a reaction. Drugs are of little value except as palliatives. The most popular are ephedrin and epinephrin sprays which not only reduce the edema and hyperemia but also control the hypersecretion. Cocaine is also popular but should never be administered except in the most desperate cases on account of the liability of establishing a habit.

It has been mentioned above that histamine or a histamine like substance may play an important role in allergic reactions. It was thought therefore that histaminase might be effective in many of these conditions. This however has not been borne out by experience. On the other hand many so called antihistamine substances have been introduced into our armamentarium. At the present there are some thirty two or more of these of which benadryl and pyribenzamine are examples. One cannot be too dogmatic as to their usefulness. Many cases of hay fever and urticaria seem to be benefited in a more or less striking degree while in others they fail entirely. Furthermore there cannot be claimed to be a constant specificity for any one of them in a particular type of reaction.

### **Vasomotor Rhinitis (Perennial Coryza)**

This is in every way identical with hay fever except that the condition persists either continuously or intermittently throughout the year and is therefore not due to pollens. The most common causes are infections of the upper respiratory tract or air borne dusts from animals birds cereals fabrics, grains tobacco or other substances. Another group of causes comprises foods and drugs and it is sometimes difficult to be certain whether these exert their effect during the time they are in the mouth or through absorption from the gastrointestinal tract. Those producing this result have already been mentioned under the general causes of allergy. Definite anatomical changes are present in these chronic conditions either of the mucous membrane of the nose and nasopharynx, or in the accessory sinuses. Histological examination will show edema and infiltration with many small round cells and eosinophiles. It has commonly been called infective rhinitis and in infectious background is undoubtedly often present.

**Diagnosis**—The diagnosis of these conditions is seldom difficult, but the cause is often more elusive than in the case of frank hay fever. The treatment is similar although the aid of a rhinologist to treat the local anatomical condition is often of great advantage. Autogenous vaccines, if the infecting organism can be determined, sometimes give good results, especially when there is also asthma.

### Asthma

**Definition**—Asthma consists of acute paroxysmal or more prolonged attacks of dyspnea due to bronchial and bronchiolar respiratory obstruction.

**Etiology**—It is a clear cut anaphylactic reaction in the respiratory mucous membrane, and is characterized by edema, hyperemia, hypersecretion and exudation and contraction of the circular bronchial muscles. It may be caused by hypersensitivity to the many substances mentioned in the early parts of this chapter. Familial indications of allergy are common in these people as well as a personal history of other forms of allergy in past years.



Fig. 11.—Photograph of bronchial plugs expectorated in a case of asthma. Compare with Fig. 10.

**Symptoms**—In the acute type the onset is explosive. As soon as the individual is exposed to the precipitating factor there is rapid onset of dyspnea which may be so severe with deep purple cyanosis as to suggest acute suffocation. The extraordinary muscles of respiration are brought into play and are assisted by the individual's grasping some firm object. Inspiration is an obviously forcible act and expiration is conspicuously prolonged. In a short time the thorax approaches the position of full inspiration the reason being that the act of inspiration is more effective than the more passive expiration. In the early stages the respiratory volume is increased but as the minutes pass the lungs may be so distended and the inspiratory effort so ineffectual that it declines in amount. Unless this condition is relieved unconsciousness with muscular twitches and then convulsions probably due to intense anoxemia may result. All paroxysms are not as severe

**Specific Treatment**—If the proper pollen can be determined, vaccination against the cause is sometimes successful. This is accomplished by giving minimal injections of the pollen extract in increasing amounts, beginning some ten to twelve weeks before the expected onset of the disease. The amount to be given will depend upon the sensitiveness of the individual. The greater this is, the smaller should be the initial injections. One should not be too optimistic as to the results. Asthma due to pollen is usually greatly benefited but for hay fever the results are not as good, and at best are temporary after one course of treatment. If the patient should seek relief immediately before an attack is expected or during one, it is well worth while to give a series of inoculations, but these should be of very small amounts. The best method of specific treatment is to continue the inoculations throughout the year giving an injection every two to three weeks and with the maximal amount that the patient can tolerate without producing a reaction. Drugs are of little value except as palliatives. The most popular are ephedrin and epinephrin sprays which not only reduce the edema and hyperemia but also control the hypersecretion. Cocaine is also popular but should never be advised except in the most desperate cases on account of the liability of establishing a habit.

It has been mentioned above that histamine or a histamine like substance may play an important role in allergic reactions. It was thought therefore that histaminase might be effective in many of these conditions. This however has not been borne out by experience. On the other hand many so called antihistaminic substances have been introduced into our armamentarium. At the present there are some thirty two or more of these of which benadryl and pyribenzamine are examples. One cannot be too dogmatic as to their usefulness. Many cases of hay fever and urticaria seem to be benefited in a more or less striking degree while in others they fail entirely. Furthermore there cannot be claimed to be a constant specificity for any one of them in a particular type of reaction.

### **Vasomotor Rhinitis (Perennial Coryza)**

This is in every way identical with hay fever except that the condition persists either continuously or intermittently throughout the year, and is therefore not due to pollens. The most common causes are infections of the upper respiratory tract or air borne dusts from animals, birds, cereals, fabrics, grains, tobacco or other substances. Another group of causes comprises foods and drugs, and it is sometimes difficult to be certain whether these exert their effect during the time they are in the mouth or through absorption from the gastrointestinal tract. Those producing this result have already been mentioned under the general causes of allergy. Definite anatomical changes are present in these chronic conditions either of the mucous membrane of the nose and nasopharynx, or in the accessory sinuses. Histological examination will show edema and infiltration with many small round cells and eosinophiles. It has commonly been called infective rhinitis and an infectious background is undoubtedly often present.

fact in many cases of asthma an allergic basis cannot be established but on psychological exploration a definite psychosomatic pattern can be revealed.

**Pathological Anatomy**—The anatomical changes in persons who have died of an acute paroxysmal asthmatic attack are similar to those dying of a serum accident or anaphylactic shock. There are intense pulmonary emphysema, edema of the lungs and other tissues, and cardiac dilatation, and in addition the ordinary signs of asphyxia. In chronic asthma the emphysema is anatomical and permanent. There are hypertrophy and dilatation of the heart, particularly the right ventricle. The mucous membrane of the bronchi and bronchioles is thickened and edematous and there is evidence of a productive lesion in the submucosa with eosinophilic infiltration. The bronchial tree may be completely plugged with a tenacious exudate. The nasal, nasopharyngeal and paranasal sinuses may show a productive lesion similar to that found in the nonseasonal hay fever. Indeed, chronic rhinitis and sinusitis are commonly associated with asthma.

**Course**—In long standing cases of asthma anatomical bronchial and pulmonary changes frequently develop. There are permanent emphysema and signs of chronic bronchitis, and if there should have been one or more attacks of lobar or bronchopneumonia atelectasis and bronchiectasis may be found. In other words the functional allergic condition may become insignificant compared to the permanent anatomical changes. Death from asthma is not common but when it does occur it is usually due to suffocation from the numerous bronchial plugs or to circulatory collapse from anoxemia. It is well to be cautious in proceeding with nose and throat operations for the removal of foci of infections or polypi during the time when a patient is suffering acutely from the disease. There may be precipitated a most violent and often fatal status asthmaticus leading to suffocation and collapse.

**Diagnosis**—The diagnosis of an acute attack of asthma presents little difficulty. The first episode may be confused with bronchiolitis or severe bronchitis but the numerous dry rales and the obvious interference with respiration are quite distinctive. In the more chronic cases chronic bronchitis, emphysema and sometimes bronchiectasis make it difficult to assess how much of the symptomatology is due to these and how much to asthma. In time the asthmatic features may disappear. Acute right ventricular cardiac failure may also confuse the picture as this is not an unusual sequela to long standing asthma. In these cases it is important to appreciate that the cardiac factor may be of greater importance than the asthma. Rarer conditions to be differentiated are bronchial obstruction from bronchogenic carcinoma or mediastinal tumors.

**Treatment**—The treatment of the immediate attack is best accomplished by giving 0.5 to 1 cc (7 to 15 minims) of a 1:1000 solution of epinephrin subcutaneously. This usually gives prompt relief and it can be repeated as often as required. Some have advocated the repeated use of small doses of ephedrin several times a day to prevent or at least modify the severity of the attacks from their beginning. This drug has been disappointing in the treatment of the acute attacks once they have been established. Morphia  $\frac{1}{8}$  to  $\frac{1}{4}$  grain hypodermically,

as this description implies. Many of them are comparatively mild, but may follow each other in rapid succession while in other instances there may be long intervals between them. There is cough, often associated with expiration, which to some extent aids this act. The sputum is usually scanty and tenacious, consisting of thick, viscid mucus which may form a cast of the smaller bronchi, and when expectorated is in the form of branching plugs or spirals (Curschmann's) (see Fig. 511). The sputum, in addition to this mucous contains eosinophiles and Charcot-Leyden crystals. It is rare that this sputum is blood stained although in severe cases a slight tinge may be noted. Edema of the lungs sometimes occurs apparently due to the great increase of pressure in the pulmonary circulation. Then the sputum becomes frothy and copious and may be frankly pink in color. A careful examination of the sputum by the physician may provide him with valuable information. In uncomplicated asthma this is composed entirely of mucus without any gross evidence of a purulent component. If this be present, it indicates an infective factor which may be primary or secondary and has an important bearing on the course and handling of the case. Pain is not a prominent symptom, but after a severe attack there may be soreness in the intercostal spaces and in the epigastrium, probably due to the violent muscular effort which has been exerted.

During the early stages of an attack when the volume of pulmonary ventilation is increased there is a lowering of the alveolar  $\text{CO}_2$  and an acute uncompensated gaseous alkalosis may result with alkaline urine and tetany. In the later stages a  $\text{CO}_2$  retention may occur. The first stage is important because if prompt relief is given and the cyanosis rapidly relieved there may be long periods of apnea, and frequently periods of Cheyne-Stokes breathing.

The physical signs are quite characteristic and consist of numerous bilateral dry rales of all sizes. They are audible without a stethoscope and can be palpated. In addition the percussion note is hyperresonant due to a transitory overdistention of the alveoli. The cardiac dullness may be obliterated and the heart sounds distant with accentuation of the second pulmonic sound. In the blood there is often found a slight leucocytosis due to an eosinophilia.

The cause of the symptoms and signs is the irregular narrowing of the lumina of the bronchi and bronchioles due to swelling of the mucous membrane and contraction of the circular muscles. This as already mentioned is a purely allergic effect. The eosinophiles and Charcot-Leyden crystals in the sputum and the eosinophilia are also indicative of this.

The precipitation of an attack is due to exposure to the specific causative agent but this susceptibility may be enhanced by mental or psychic stimulation, physical exertion, exposure to cold or heat, irritating gases or atmospheres, sexual excitement and a host of other external or environmental stimuli. In other words there are again to be found the two possible factors: the susceptibility to a specific substance and the increase of this susceptibility by nonspecific conditions.

At one time asthma was considered as a purely neurotic condition. With the introduction of the allergic concept the emotional factors were almost completely neglected. There has now, however, been a return to a broader concept which may be applied to many so-called allergic phenomena. In

to the direct action of foodstuffs upon the gastrointestinal mucous membrane as in the contact dermatitis. Gastric hemorrhages of an allergic origin have also been described. The sequence of events in these cases is not always clear but it is well to bear the possibility in mind. The similarity of mucous colitis and bronchial asthma has already been referred to (see Chapter X).

### Physical Allergy

It is not infrequent that one is consulted by patients who claim that on exposure to cold they develop a syndrome which from its description strongly suggests an allergic reaction. For instance, when the hands are immersed in cold water urticaria develops, and it will frequently be found if cold water or a piece of ice is placed on some other portion of the skin, urticaria will develop over the localized area of its contact. Some persons are so sensitive that they cannot take a cold bath as following this the urticaria is diffuse and collapse symptoms may occur. Similarly exposure to cold air although the body is covered, may produce an attack of asthma or acute rhinorrhea. Others on swallowing cold drinks or foodstuffs, as ice cream, may also develop acute prostration, tremors, asthma, urticaria, or other allergic phenomena.



Fig. 51.—Urticaria hi nails the type due to cold. The area affected does not extend beyond the area directly exposed to ice. (Courtesy of Dr. W. W. Duke. From Sutton and Sutton. Diseases of the Skin.)

There is also a group of persons who respond to the opposite thermal insult namely, when they are exposed to hot weather drink hot liquids or eat hot foods, they have similar reactions. The more difficult ones to isolate are those who are so sensitive that the warmth produced by mental, physical sexual or psychic excitement precipitates an attack.

Persons who are sensitive to the solar spectrum also compose an interesting group. It does not follow that every case is sensitive to the same wave lengths which may add to the confusion but there are people who when exposed to sunshine develop urticaria dermatosis even dermatitis and some times alarming collapse.

It is these cases of physical allergy which are hard to explain upon the usual precipitin basis and they would point much more directly to some histamine or histamine like reaction.

### Paroxysmal Hemoglobinuria

Closely associated with the allergic reactions due to cold is paroxysmal hemoglobinuria. This apparently results from the production of a hemolysin

is of value in mild cases but should be given with great caution as it may relieve distress but hasten respiratory failure. Tincture of stramonium with potassium iodide has been a favorite remedy, and in many cases gives relief, particularly when taken over prolonged periods. Ipecacuanha is of particular benefit in children, as it assists them through the act of vomiting, in ridding the trachea and upper bronchi of the tenacious mucus. Belladonna and atropin have little antispasmodic effects in these cases. Trisentine sometimes gives prompt relief. What was written concerning antihistamine drugs under Hay Fever is equally applicable to asthma. It may be stated, however that benadryl has a certain advantage in addition to this action namely a sedative effect which indicates it may be given at bedtime and during the night to assist in obtaining a restful sleep which is often a problem difficult to solve.

The general handling of the case is important. All the normal functions should be maintained with regularity, and the diet carefully scrutinized for any possible allergic susceptibility. The specific treatment is both prophylactic and curative. If the cause can be ascertained, the patients must by all means be kept from its contact. Inoculations as in other forms of allergy should be undertaken to reduce the sensitivity of the individual. The treatment of asthma due to infectious or focal lesions, particularly in the upper respiratory tract is fraught with great difficulty. Autogenous vaccines have been advocated and appear to be of value if reactions are produced, but on the other hand almost equally good results have been obtained from producing similar reactions by nonspecific proteins. The removal of focal infections in the upper respiratory tract should be undertaken with great caution. It has already been mentioned how there may be alarming and even fatal results from these procedures if undertaken at the improper time. When these occur epinephrin should not be spared. In fact in the most desperate cases a continuous intravenous injection of saline at the rate of 2 cc per minute to which a minimum of epinephrin is added every three to five minutes may tide the patient over an almost hopeless collapse. The amount given can be controlled by the changes in blood pressure which at the beginning will be found to be low. It should not be raised above 130 mm Hg systolic pressure. For respiratory distress and cyanosis air enriched with oxygen or a mixture of helium and oxygen should be inhaled constantly with a proper apparatus (see Fig. 63) until these symptoms are relieved. The treatment of the sequelae of asthma such as chronic bronchitis, emphysema and bronchiectasis is discussed elsewhere.

### Gastrointestinal Allergy

There have been reported groups of cases presenting acute abdominal pain, vomiting, diarrhea and collapse relieved by epinephrin. These symptoms have frequently been associated with vasomotor rhinitis, urticaria, angioneurotic edema, hay fever or asthma. Such symptoms occurring in one who is known to be allergic should be suspected as being due to this cause or in cases where no other explanation can be found, it is profitable to explore this avenue for a possible etiology. It is supposed that these attacks can be initiated in exactly the same manner as asthma or hay fever, or may be due



to the direct action of foodstuffs upon the gastrointestinal mucous membrane as in the contact dermatitis. Gastric hemorrhages of an allergic origin have also been described. The sequence of events in these cases is not always clear, but it is well to bear the possibility in mind. The similarity of mucous colitis and bronchial asthma has already been referred to (see Chapter X).

### Physical Allergy

It is not infrequent that one is consulted by patients who claim that on exposure to cold they develop a syndrome which from its description strongly suggests an allergic reaction. For instance, when the hands are immersed in cold water urticaria develops, and it will frequently be found if cold water or a piece of ice is placed on some other portion of the skin, urticaria will develop over the localized area of its contact. Some persons are so sensitive that they cannot take a cold bath, as following this the urticaria is diffuse and collapse symptoms may occur. Similarly exposure to cold air although the body is covered, may produce an attack of asthma or acute rhinorrhea. Others on swallowing cold drinks or foodstuffs, as ice cream may also develop acute prostration, tremors, asthma, urticaria, or other allergic phenomena.



Fig. 51.—Urticaria (hives) due to cold. The area of the wheal does not extend beyond the area directly exposed to ice. (Courtesy of Dr. W. W. Duke from Sutton and Sutton. Diseases of the Skin.)

There is also a group of persons who respond to the opposite thermal insult namely when they are exposed to hot weather drink hot liquids or eat hot foods they have similar reactions. The more difficult ones to isolate are those who are so sensitive that the warmth produced by mental, physical sexual or psychic excitement precipitates an attack.

Persons who are sensitive to the solar spectrum also compose an interesting group. It does not follow that every case is sensitive to the same wave lengths which may add to the confusion but there are people who when exposed to sunshine develop urticaria, dermatosis, even dermatitis and sometimes alarming collapse.

It is these cases of physical allergy which are hard to explain upon the usual precipitin basis and they would point much more directly to some histamine or histamine like reaction.

### Paroxysmal Hemoglobinuria

Closely associated with the allergic reactions due to cold is paroxysmal hemoglobinuria. This apparently results from the production of a hemolysin

when the patient is exposed to a certain temperature. In addition to the appearance of a "bloody urine" (really hemoglobinuria) there may be pyrexia, shivering, malaise, and headache, and sometimes collapse. The attacks may be initiated either by submerging part of the cutaneous surfaces, such as the hands in cold water or taking a cold bath. This type is called 'hemoglobinuria frigoris' and it is only in such cases that the Donath Landsteiner reaction is positive. Sympathectomy has been advocated as a therapeutic measure. The exact manner of production of the hemolysis is not understood. It is a striking feature, however, that practically all of the cases reported have either given a positive Wassermann reaction, or anatomical evidence of myphalus. There are other types, namely, hemoglobinuria on exertion, nocturnal hemoglobinuria associated with hemolytic anemia, and paralytic hemoglobinuria when the pigment is methemoglobin associated with paralysis of the skeletal muscles.

### Miscellaneous Allergic Reactions

It would not be within our province to cover in detail all the conditions that have been ascribed as possibly due to allergy. There is, however, one large group which, in addition to urticaria and angioneurotic edema, may assume a variety of dermatological patterns, such as eczema, erythemas, pruritus, prurigo, lichen, purpura, pompholyx, etc. Purpura of the Henoch type has been accused of having an allergic basis. Finally, there are those who suffer from migraine of unexplained origin. Many of these give a familial and personal history of allergy, and intimately related to these are cases of idiopathic epilepsy. Before a case of epilepsy is finally pronounced idiopathic, the possibility of its having an allergic foundation should be explored.

### References

- Best, C. H., and McHenry, F. W. Histamine. *Physiol. Rev.* 11: 371, 1931.  
 Bullock, W. Angioneurotic Edema, The Treasury of Human Inheritance (Eugenics Laboratory Memoirs IX) Part 3, 38, 1939.  
 Coca, A. E. Hypersensitivity. *Texts in Practice of Medicine*. New York, 1940. W. F. Prior Co., Inc.  
 Cooke, R. A. The Treatment of Hay Fever by Active Immunization. *Laryngoscope* 25: 103, 1915.  
 Cooke, R. A. Diseases of Allergy, Internal Medicine. Philadelphia, 1932. Lea and Febiger.  
 Cooke, R. A., and Vander Veer, A. Human Sensitization. *J. Immunol.* 1: 201, 1916.  
 Cooke, R. A. Allergy in Theory and Practice. Philadelphia, 1946. W. B. Saunders Co.  
 Crowder, J. R., and Crowder, T. R. Five Generations of Angioneurotic Edema. *Arch. Int. Med.* 20: 840, 1917.  
 Diaz, C. J. El Asma y Otras Enfermedades Alérgicas. Published by Editorial Espana, Madrid, 1943.  
 Freedman, H. J. Acute Anaphylactic Shock Following Intracutaneous Test for Sensitivity to Horse Serum. *New England J. Med.* 212: 10, 1945.  
 Goodall, E. W. Serum Sickness. *Lancet* 1: 323, 1918.  
 Huber, H. L., and Koessler, K. K. The Pathology of Bronchial Asthma. *Arch. Int. Med.* 30: 689, 1922.  
 Lane, C. G. Recognition of Occupational Dermatoses. *New England J. Med.* 227: 31, 1942.  
 Longcope, W. T. Anti-anaphylaxis and Desensitization. *Physiol. Rev.* 3: 240, 1923.

- Longcope W F Serum Sensitization and Anaphylous Reactions From Certain Drugs Particularly the Sulfonamide *Medicine* 22 :51 1943
- Opie E Significance of Allergy in Disease, *Medicine* 15 :49 1936
- Osler W On the Visceral Manifestations of the Erythema Group of Skin Diseases *Am J M Sc.* 127 :1 1904
- Pransnitz C and Kustner H Studien über die Leberempfindlichkeit *Zentralbl. f. Bakt.* 86 :160 1911
- Quincke H Ueber akutes umschriebenes Hautodem *Monatsshefte f. prakt. Dermat.* 1 :129 1881
- Rackemann F M Clinical Allergy New York 1931, The Macmillan Co
- Rackemann F M Clinical Allergy Particularly Asthma and Hay Fever New York 1931 The Macmillan Co
- Rackemann F M Allergy: a Review of the Literature of 1944 and 1945 *Arch. Int. Med.* 78 :108 1946
- Rich A R and Gregory J E Experimental Demonstrations that Eosinophilia Nodosa Is a Manifestation of Hypersensitivity *Bull. Johns Hopkins Hosp.* 73 :10 1943
- Roche Bram Studies on Blood Histamine in Patients With Allergy II Alterations in the Blood Histamine in Patients With Allergic Diseases *J. Clin. Investigation* 20 :419 1941
- Schloss O M Allergy to Common Food *Am. J. Dis. Child* 3 :341 1912
- Schwartz I and Fleck S M Dermatitis and Dermatitis New York 1946 Paul B Hoeber Inc
- Selye Hans The Alarm Reaction *Cyclopedia of Medicine, Surgery and Specialties Philadelphia* 1940 F A Davis Co
- Vaughan W T Allergy and Applied Immunology St. Louis, 1941 The C V Mosby Co
- Von Pirquet C F and Schick B Die Serumkrankheit Leipzig und Wien 1900 Franz Deuticke.
- Weaver G H Serum Disease *Arch. Int. Med.* 3 :435 1909
- Wolff Eisner A Das Heufieber sein Wesen und seine Behandlung München 1906 J F Lehmanns Verlag

## CHAPTER XXII

### DISEASES DUE TO ABNORMAL ENVIRONMENTS

#### INTRODUCTION

Through the vicissitudes of life the human body is called upon from time to time to cope with environmental conditions which cannot be considered a usual when compared with its normal or average surroundings. The principal physical changes of environment are those of temperature and barometric pressure. The human body has the facility of accommodating itself to wide variations in these conditions. In addition the inspired air may be deficient in its most important constituent—oxygen—or may contain harmful gases and other substances. Even to many of these conditions the body may develop a certain degree of protection particularly if it is exposed to them gradually or can get rid of them with greater facility than they are absorbed. The results of harmful changes of environment can hardly be called diseases although they may produce death. They are rather changes in the physico-chemical relationships in the body to which it cannot adapt itself with sufficient rapidity. Whereis some of them, like exposure to intense heat and cold have been overcome in great measure by modern knowledge others which a century ago were not conceived as possible such as diving to the depths of the sea and climbing close to the stratosphere are now matters of everyday occurrence. These adventures have enlightened us as to what the animal organism can do in accommodation, and have also taught us means of preventing their deleterious effects.

#### EFFECTS OF HEAT

The response of the human organism to an increase of its thermal environment depends upon a number of factors in addition to the actual level of the thermometer. There must be considered the degree of humidity and the movement of air currents or cooling power of the atmosphere in which the body is immersed. If the temperature of the environment is equal to or greater than 98° F. heat loss cannot be accomplished by radiation and conduction but is assisted by evaporation of water by sweating and increased pulmonary ventilation. The former is assisted by active air currents either naturally by winds or artificially by fans. If the atmosphere is saturated with aqueous vapor this evaporation cannot take place and it has been determined by Haldane that at rest in such a saturated atmosphere the body temperature of man increases per hour one degree at 89° F. two degrees at 94° F. and four degrees at 98° F. With physical exertion under similar environmental conditions a proportionate increase of body temperature will occur depending upon the increase of oxygen consumption. In general any of these conditions or a combination of them which lead to retention of heat will raise the body

temperature. The clinical response to this change in the internal environment varies considerably in different people and may produce somewhat different symptom patterns. Conditions which increase the response or susceptibility are old age, fatigue, alcoholism, obesity, and circulatory diseases. Exposure over periods of time may bring about a certain tolerance. Loss of water and sodium chloride through sweating also may modify the effects, particularly if at the same time there is a copious intake of water. The tissues become hypotonic through loss of salt which is not replaced. This produces "water poisoning," which will be considered below (see Heat Cramps).

**I Moderate Pyrexia (Heat Retention)**—When the body temperature rises several degrees there are a throbbing headache, tachycardia, dyspnea and restlessness. Sweating decreases and there is a polyuria. This is one of the dangers in hyperthermic therapy.

**II Heat Cramps (Water Poisoning)**—This is due to a hypotonic state of the body owing to a relative increase in sodium chloride loss through the sweat. There may indeed be a concentration of the blood and a diminished blood volume. It usually occurs in stoelcholds, deep mines and other hot environments. It is characterized by muscular twitchings and cramps abdominal colic, nausea, vomiting and diarrhea. Respiration may be embarrassed through intercostal and diaphragmatic spasms. It closely simulates a mild form of tetany. It is aggravated by drinking water, beer or other liquids. The experienced workers have learned or it has been handed down by tradition certain prophylactic measures such as the custom of miners in deep hot mines of taking into the pit a mixture of oatmeal and salt which they munch during their work or as stevedores and rolling mill workers liberally add salt to their beer. Likewise the condition is promptly relieved by the intravenous injection of a liter of hypertonic (1.5 per cent) salt solution.

**III Heat Exhaustion**—If heat retention exceeds a moderate degree the symptoms all become much aggravated. Sweating ceases and the skin becomes cold, damp and pale but the rectal temperature is increased although the mouth readings may be normal and the axillary temperature decreased. In addition to the symptoms mentioned in I above there are pronounced nervous manifestations—vertigo, ataxia, visual impairment, dilated pupils and great exhaustion. The treatment consists of rest and cool surroundings.

**IV Sunstroke (Hyperpyrexia, Heat Stroke, Insolation)**—This is a further manifestation of heat retention. The heat control seems to be suddenly lost and a mounting hyperpyrexia develops. Headache and signs of mild heat retention may be premonitory but the onset is often a sudden collapse with delirium followed by unconsciousness and coma. The skin instead of being cool and damp is hot and dry, the pupils are contracted, tachycardia is 170 to 190, respirations are deep almost of the type caused by acidosis and periodic breathing is the rule in the most severe cases. The rectal temperature may show readings of 106° to 110° F. Purpura often occurs and there is complete flaccidity although in the early stages muscular twitchings and cramps as in II may be detected. This condition has a high mortality and accounts for the frequent deaths in the heat waves recorded each summer.

The treatment consists of maintaining the skin circulation by constant friction and promoting heat loss at the same time by playing a spray of cold water over the whole body in the presence of air currents produced by fans. Cold packs with sheets may be substituted for the spray. Friction of the skin by sponges or gauze pads should be continuously employed. It is most important that surface vasoconstriction should not occur. Experienced stokers have known a homely prophylactic measure, which consists in wearing a heavy flannel shirt saturated with sweat and water, which perpetuates the cooling effect of evaporation, and simulates the water skins hung in the open air in hot desert regions. Ice packs and ice baths, formerly used lead to vasoconstriction of the cutaneous vessels, and thus reduce heat loss and raise the visceral temperature.

The body temperature should not be reduced below  $102^{\circ}\text{F}$ , for secondary hypopyrexia may be induced by too rapid heat loss. Dehydration and salt loss should not be neglected. They may be corrected by intravenous hypertonic saline injections. A moderate pyrexia may persist for several days, but after 36 hours of temperature control recovery is the rule. Mental symptoms may persist for some days or weeks, and headaches may be distressing for many months. A person once the victim of heat stroke may for years become restless and apprehensive with a mounting thermometer. It is difficult to be certain how much of this is due to fear and how much is a residue of the thermal shock or a hypersensitiveness to heat (see Heat Allergy).

### EFFECTS OF COLD

Exposure to a moderate degree of cold stimulates the oxygen consumption and thus raises the basal metabolism in this environment. This has been found to be constant in people who live in the arctic regions as compared with those in the temperate zones and there is again higher than that of inhabitants of the tropics. But this is a physiological response to a normal environment, and the heat loss would be easily regulated. From 70 to 80 per cent of heat loss occurs through the skin and this is accelerated as the surface temperature is reduced. Compensation is brought about by constriction of the skin vessels, thus causing less blood to be brought to the surface for cooling while shivering and increased muscle tonus produce more heat. Thus there are reduced heat loss and increased production. If however this compensation is not effective and the body temperature of a warm blooded animal falls below  $68^{\circ}\text{F}$  death is certain. Even at higher temperatures the outcome is dubious. The lowest temperature recorded in man with recovery is  $75^{\circ}\text{F}$ .

All people are not equally susceptible. Infants and the elderly are particularly so while the virile and more robust particularly the well nourished are much less affected. The most important predisposing factors to pathological lowering of the body temperature in a cold environment are inadequate clothing, shortage of food, muscular fatigue and alcoholism. The last acts through producing imperfect nervous thermal control and somnolence.

**Symptoms**—The first symptoms are shivering and increased muscle tone. There are mental alertness and a desire for exercise but when the body tem-

perature begins to fall, this is followed by muscular fatigue, weakness, stiffness and drowsiness with an almost uncontrollable desire to sleep which, if given way to, drifts into coma. These all indicate a lowering of heat production as well as a continued heat loss and the oxygen consumption declines as in a cold blooded animal. Death eventually occurs.

**Treatment**—The best treatment is absolute rest and elevation of the body temperature by a warm environment. This is effected by wrapping the person in warmed blankets in a heated room. If these are not available a similar purpose may be attained by keeping the victim in close contact to other persons or animals and protected from the wind. Hot water bottles and hot bricks should be used with caution, as the ischemic skin is easily burned. Sips of hot beverages at short intervals help to increase the body temperature. The person may appear to be alive but irreparable damage has been done and he may die later. If not complete recovery occurs.

Allergic reaction to cold and local lesions (frostbite) are considered elsewhere.

### EFFECTS OF HIGH BAROMETRIC PRESSURE

**Synonyms**—Compressed air illness, caisson disease, divers palsy, the bends.

**Etiology**—The effects of increased barometric pressure are due not to the pressure itself but to the physical effects this has on the solution of gases in the blood by way of the lungs. The ordinary barometric changes met with in our daily life do not produce the effects to be described. The solution of gases in a fluid depends upon their partial pressures (Dalton's law). Any increase of these pressures in man's normal environment is negligible, therefore no symptoms are produced.

Men working in caissons as in building tunnels and as divers, are exposed to an environment where the barometric pressure may be raised to ten or fifteen atmospheres. The oxygen and nitrogen go into solution in the plasma and eventually saturate the tissues in accordance with their partial pressures, therefore at five or eight atmospheres pressure there will be five or eight times as much in solution in these tissues. This applies both to oxygen and nitrogen, but in subsequent events the former is readily handled by the hemoglobin and tissues while the nitrogen being a foreign element except at normal pressures causes the symptoms and lesions. All tissues do not absorb nitrogen at the same rate nor to the same amounts. Fats absorb five times as much as water and therefore take a relatively long time to become saturated. Tissues with tardy or limited blood flow such as the ligaments, bones, spinal white matter, liver and spleen come into equilibrium gradually. But at the best of times it takes some hours even with the increased circulation rate of physical work for the entire body to come into equilibrium at the new level. During this period no symptoms are produced but the duration and amount of pressure determine the degree of saturation of the tissues.

As soon as the barometric pressure is reduced the nitrogen in the blood is readily given off into the alveolar air and at the same time nitrogen comes out of solution from the tissues. As its absorption and saturation of tissues were

irregular so will be the desaturation. Physical exercise will accentuate and localize the effect to the group of muscles or limb which is most used. If the decompression is not done properly bubbles of nitrogen will form in the tissues, the capillaries and small veins, and venules. This will be particularly prominent in the fat deposits, white matter of the brain and cord and other tissues where the saturation is high or the blood flow is slow. These bubbles or air emboli compress or rupture the tissues, particularly where they are most numerous and largest. Hemorrhages and obstruction of the blood flow are common.

**Symptoms**—The symptoms in such a widely distributed and irregular disturbance will be variable and bizarre. They usually appear an hour or so after the faulty decompression has been completed, although in severe cases a few minutes only may elapse. There are pains in the joints muscles and ligaments (hence the bends), abdominal cramps, nausea, vomiting and a great variety of nervous phenomena including dizziness, syncope deafness, paralysis or paresis, particularly of the legs, loss of sensation and more rarely hemiplegia, paraplegia or monoplegia. The more rapid the onset, the more serious and widespread are the symptoms, and the more likely is death to occur. In these cases pulmonary and coronary emboli and frothy blood in the cardiac chambers may be found. Fortunately most cases are comparatively mild. The condition is most severe in fat men and even plump men should not be allowed in high pressure caissons.

**Treatment**—The best treatment is prophylaxis which depends upon proper decompression. The older method was by gradual but steady reduction of the pressure. In 1906 Haldane introduced the method of reducing the pressure in stages. It is not only safer but also more rapid. He found that rapid decompression of atmospheric pressure from two atmospheres to one could be accomplished without danger. Decompression is not safe if the pressure of nitrogen inside the body is much more than twice that of the atmospheric nitrogen. Therefore the first step is to reduce rapidly the absolute pressure to one half. A time interval is then allowed to elapse during which the body comes into equilibrium. The pressure is again reduced by half with another interval and so on down to one atmosphere (normal pressure). The duration of the intervals depends upon the maximum pressure and the duration of the exposure. If symptoms appear after the decompression is completed, the person must be immediately recompressed to at least three atmospheres of pressure and the stages repeated with longer intervals.

### EFFECTS OF LOW BAROMETRIC PRESSURE

The percentage of oxygen in the atmosphere is not the sole factor which affects respiratory function. It was mentioned in Effects of High Barometric Pressure that gases are soluble in accordance with their partial pressures. This is equally true in regard to the combination of oxygen with hemoglobin and its solubility in the plasma. Therefore a lowered oxygen percentage under high barometric pressure may combine with hemoglobin to form oxyhemoglobin in the same amounts as when there are a normal percentage and pressure.



It is these factors in the alveolar air which determine the partial pressure of oxygen to which the blood in the capillaries is exposed

In making these calculations allowance must be made for the partial pressure of the aqueous vapor in the alveolar air and in the following examples this will be kept constant at 47 mm H<sub>2</sub>O

I Normal O<sub>2</sub> percentage with normal pressure

$$\frac{15\% \text{ O}_2 \times (760 \text{ mm} - 47 \text{ mm})}{100} = 101.9 \text{ mm partial pressure O}_2$$

II Low O<sub>2</sub> percentage with high pressure

$$\frac{7\% \text{ O}_2 \times (760 \text{ mm} - 47 \text{ mm})}{100} = 10.3 \text{ mm partial pressure O}_2$$

III Normal O<sub>2</sub> percentage with low pressure

$$\frac{15\% \text{ O}_2 \times (380 \text{ mm} - 47 \text{ mm})}{100} = 50 \text{ mm partial pressure O}_2$$

IV Low O<sub>2</sub> percentage with normal pressure

$$\frac{7.5\% \text{ O}_2 \times (760 \text{ mm} - 47 \text{ mm})}{100} = 50 \text{ mm partial pressure O}_2$$

In the present discussion we are concerned with III and IV

Normal oxygen percentage and low barometric pressure (III) is met with in high altitudes, aeroplane flights and balloon ascensions. Low oxygen percentage and normal barometric pressure (IV) is encountered at times in mines, tunnels, wells, submarines, etc. The net result in both is the same, namely a reduction in the percentage of oxyhemoglobin in the arterial blood. There is one important point always to be taken into consideration—the rate at which the lowering of the partial pressure of O<sub>2</sub> is produced. If this be sudden the onset of symptoms is rapid and severe, while if it be slower, covering several days or weeks, acclimatization usually takes place and this is particularly obvious in persons who have been accustomed to lowered partial pressure.

The symptoms are the same under all circumstances, the only variation being dependent upon the rapidity of exposure, the degree of lowered partial pressure and the susceptibility or acclimatization of the individual. They are headache, vertigo, dyspnea, palpitation and cyanosis, particularly on exertion, mental irritability and weakness. Hyperpnea is obvious and causes a decreased alveolar CO<sub>2</sub> percentage. There may be only slight nausea but explosive vomiting is characteristic and closely resembles that in seasickness. It is commonly stated that epistaxis and bleeding from the ears are features. If they occur, they are due to the lowered barometric pressure and not to the reduced oxygen pressure. They may occur in rapid and high aeroplane or balloon ascents but in ordinary altitudes of mountains they are rare and some other cause should be looked for. Those who remain at a high altitude or work constantly in a low oxygen partial pressure rapidly develop a polycythemia and increased hemoglobin with a low color index. This is one of the most important factors in acclimatization. All the usual symptoms can be accounted for by anoxemia. If this is rapidly induced and is extreme, unconsciousness and death may result.

In the high altitudes of mountain climbing colossal feats of endurance have been accomplished as in the series of attempts to conquer Mount

Everest Mountain climbers must necessarily be in the best of physical condition and except for amateurs, or at great heights (26,000 feet), "mountain sickness" or "soroche" does not occur. On the other hand, rapid ascents by railway as at Pikes Peak, in Peru and Chih, by aeroplane or by balloon, symptoms usually develop between 8,000 and 10,000 feet in those who are not acclimatized. From this height upward the onset of symptoms varies with the individual. It is, however, important, as flying is becoming increasingly popular, to appreciate that infrequent aeroplane flights of a few hours' duration do not conspire to produce acclimatization. Even experienced pilots who fly constantly should not attempt an altitude of more than 12,000 feet without oxygen. The onset of disabling symptoms is so insidious that unconsciousness may imperceptibly supervene. But even more important than these extreme effects are the minor ones such as impaired coordination, ataxia, disturbed vision, delayed reaction time, mental confusion and physical lethargy. It is obvious since commercial flying is being conducted at higher altitudes, that every precaution should be taken to prevent these effects as they no doubt may contribute to accidents from errors in judgment and lack of control. To a large extent these effects have been circumvented by construction which permits the bromine pressure within the aeroplane to be kept at a normal level or around 760 mm Hg. Acute infectious periods of convalescence, and fatigue all reduce one's capacity for acclimatization.

This subject cannot be concluded without reference to a number of other important causes of anoxemia from lowered percentage of oxygen (IV above). These are principally encountered in mining as follows:

**1 Black Damp or Choke Damp**—This is applied to an atmosphere in a mine where there are no symptoms of acute anoxemia, but where a candle will not burn, or when the oxygen in the inspired air is reduced to about 17 per cent. Carbon dioxide may be somewhat increased, which is beneficial as it increases respiratory effort and in addition to extinction of the safety lamp, gives the miner warning of approaching danger.

**2 Fire Damp**—This is due to methane which is explosive in certain concentrations but for our present consideration it is important when it occurs in sufficient amounts to dilute the oxygen to a dangerous degree.

**3 'After Damp'** indicates the presence of carbon monoxide. This will be discussed in a separate section.

**4 White Damp**—This is a mixture of carbon monoxide and steam in the air of a mine and is due to the heat produced by spontaneous oxidation of coal. Its danger lies in the presence of carbon monoxide.

The most common of the foregoing is 'black damp' from the point of view of lowered O percentage. This condition may be present in wells, subterranean passages, long sealed cellars built in rock, abandoned mines and caves.

**Treatment**—The treatment of "mountain sickness" is rest and in emergencies, enriching the inspired air with oxygen. But the latter does not help to acclimatization and if the patient is obviously seriously affected, return to a lower level is imperative. Tachypnea with rales and other signs of pulmonary engorgement or edema also demand such a move. There may be

pyrexia and tachycardia. In situations where there is a low oxygen percentage its administration or prompt removal of the patient to ordinary air is indicated. If respiration has ceased artificial respiration or the use of a respirator should be maintained for some hours before the case is abandoned as hopeless.

### MEDICAL PROBLEMS OF AVIATION

The medical problems of aviation are in great part due to rapid changes in man's physical environment to acceleration of movement in a centrifugal or centripetal direction, or to slower and more rhythmic deviations from a center of gravity. Most of these problems are met with under other conditions or occupations but are acutely prominent in aviation through the rapid and extreme changes which are here encountered. In order to avoid repetition but at the same time to focus attention on the newer aspects of these problems reference will be made to the sections where the fundamentals are considered while the specific implication will be dealt with here in more detail.

#### Acute Oxygen Want

In the previous section and on page 179 under Cyanosis the effects of low partial pressure of oxygen in the alveolar air upon the oxygen saturation of hemoglobin have been dealt with. As far as low barometric pressure was concerned this was only of medical importance in civilian life in mountain climbing and the occasional balloon ascents until the modern aeroplane was introduced. A well trained individual can ascend with fair rapidity to between 8000 and 12000 feet above sea level without much disability. But with the introduction of aeroplanes which ascend to an altitude of 40,000 feet or even higher at a speed of thousands of feet a minute new problems have arisen. It is now a question not of what the machine can do but of what man can endure. The highest altitude that man has survived in mountain climbing has been about 27 odd thousand feet (Mallory at Mount Everest). But this adventure was undertaken without oxygen being supplied. In modern warfare the altitude to which an aviator may be forced is unpredictable. Therefore, an oxygen supply for all personnel in the plane is obligatory and furthermore the mask and all its adjustments should be tested and found in proper working order before the flight is started.

The symptomatology of acute oxygen want is most treacherous through the insidious character of its onset. The first sensation may be a desire for somewhat deeper breathing. This is most obvious when the victim is doing physical work otherwise it may pass unnoticed by the less observant. At this time there may be a feeling of exhilaration which is most deceptive and often produces a false confidence which masks progressive incoordination and faulty judgment. These features are soon followed by lethargy and rapid onset of unconsciousness. During this period there is increasing cyanosis which in the earlier stages is frankly blue but gradually changes to a dirty greyish hue with profuse sweating which is quite similar to the facies of peripheral circulatory failure (see page 369).

It will be noted that the severe headache, weakness and vomiting of mountain sickness are not prominent features. This is quite explainable on the factor of time. In rapid aeroplane ascents the anoxemia is produced very acutely

and the higher centers and vasomotor control are affected with explosive suddenness. During prolonged flights at moderate altitudes (8,000 to 12,000 feet) these delayed symptoms and signs may be more prominent. Furthermore acclimatization is not acquired in even relatively long aeroplane journeys nor do polycythemia changes in  $\text{CO}_2$  combining power of the blood, and other biochemical changes develop.

The only known sure means of preventing these results in aviation is by enriching the inspired air with oxygen or by increasing the barometric pressure within the aeroplane. In rapid ascents this should be started before the plane leaves the runway and in slower ascents at 8,000 feet at the highest. It is safer however, to have no exceptions. The aviator in war is, as a rule, relatively youthful and youth is adventurous. He does not tolerate additional encumbrances gladly and may consider himself above the laws of biophysics. It is true that there is a zone of altitude (8,000 to 12,000 feet) in which men vary as to their susceptibility, but this is too narrow to be of much practical significance. Therefore, rigid discipline in the use of oxygen should be enforced.

### Chronic Oxygen Want

It is a common observation that all people do not equally tolerate residence at high altitudes. There are here excluded those who from some physical defect, apparent or masked suffer from insomnia extrasystoles respiratory oppression weakness or dizziness at such elevations as 1,000 feet. The causes for these are not clear as the degree of oxyhemoglobin desaturation is negligible. Rather we shall consider those who when first reaching 8,000 to 14,000 feet either have mountain sickness and soon recover or are very little troubled with symptoms. In either case they may shortly acquire acclimatization not only as regards symptomatology but also biochemical and hematological factors. In time, usually some months they develop irritability of temper, decreasing power of mental concentration easy fatigability menstrual irregularities lessened libido and a host of other minor complaints (see *Neurocirculatory Asthenia* page 373). It is presumed that these symptoms are due to chronic oxygen want. This is probably so as no other common factor can be found.

A similar train of symptoms may be found in aviators particularly those who frequently attain very high altitudes. There is however an important difference. The residents of high altitudes really do have a constant oxygen want while the aviator with a proper oxygen supply can ascend to 35,000 feet without any noticeable oxygen lack. It may however be slight and oft repeated and with the addition of the stress and strain of flying over enemy territory open water anti aircraft barrages in intense cold with poor visibility and constant noise of considerable decibels a summation of factors is operative toward producing that elusive quality called chronic fatigue.

Whatever be the cause it is a very real problem in aviation which comes entirely within the realm of the Medical Officer. The only cure is a period of grounding with a change of environment conducive to physical and spiritual rehabilitation which is usually successful. Salvage is important both for man and machines.

It is now well known that it cannot be produced experimentally in man in the quietness of a low pressure chamber with adequate oxygen supply even over periods of many hours and days for weeks.

### Low Barometric Pressure

The effects of rapid changes of barometric pressure apart from a strictly physical problem of solution of gases have been dealt with under crisson disease (see page 1457). In aviation the course of events is somewhat reversed. In the former the victim proceeds from a higher positive pressure to a normal pressure, while in the latter it is from a normal pressure to a rapidly diminishing one. Speed is here the more important factor in precipitating these ill effects. They are not as disabling as in 'bends' but they are inconvenient in a number of ways. The gastric and intestinal gases expand according to the usual laws of physics and lead to esophageal eructations, anal explosions, a sense of abdominal tenseness and may even embarrass respiration through pressure on the diaphragm. In more extreme cases there is a sensation of crackling in the hands and muscle cramps particularly on exercise. The cerebral, spinal and myocardial effects are seldom seen. Although at the present time it is a minor disability in aviators it must be given serious consideration in anticipation of more rapid and higher altitudes and therefore certainty of closer approximation to crisson disease.

### Acceleration

The aviator particularly under combatant conditions must often change the direction of his flight with great suddenness. This may produce, therefore, considerable centrifugal force upon the internal anatomical structures if the force of gravity is operating toward the periphery or away from the thorax and head if it be the opposite it is toward the thorax and head and away from the extremities. This force is determined by a simple equation according to Newton's law  $F = M \times a$  therefore  $a = \frac{F}{M}$  when acceleration is proportionate to force and inversely proportionate to mass. In curved flight the acceleration effect depends upon the rate of change of direction and the speed. It can be expressed in the formula  $F = \frac{M V^2}{r}$  ( $V$  = velocity,  $M$  = mass and  $r$  the radius). It has become customary to express this unit as so many 'Gs' comparable with the number of times greater or less than gravity.

It is not our purpose to enter into this further but to proceed to describe the effects of these variations in acceleration.

### BLACK OUT

When an aviator comes out of a power dive or any similar maneuver which will effect a centrifugal force there are certain well known effects. The force of gravity depending upon its intensity drives the blood to the periphery which will be to the abdomen legs and—to a less extent—the arms. There is therefore an acute cerebral ischemia the diaphragm is forced downwards respiration is embarrassed and abdominal tension is increased. The most important effect is a temporary but often disastrous loss of consciousness. This

usually occurs at 5 + G's. The methods to overcome this have now been well worked out. They consist in principle in so encasing the operator at an automatic barometric normal environment through suitable clothing or in so conditioning the aeroplane that these changes in centrifugal force are not effective. For further discussion of these particular problems the reader is referred to standard texts and journals on "aviation medicine."

### Red Out

When the acceleration is in the opposite direction the blood is driven toward the head and the diaphragm is fixed in extreme expiration. The latter is of little importance as the diaphragm is a powerful inspiratory organ. The effect on the circulation, however, is profound. Instead of the cerebral arteries and veins being almost empty and collapsed, they are full to the point of distention. There is extreme headache of a bursting character, the vision becomes blurred as through a red mist (hence the name) and hemorrhages into the conjunctiva, retina, inner ears, nasopharynx and, most important into the contents of the closed cranium may result. Unconsciousness may occur also but it has a riotous onset compared to the smooth oblivion of the black out. The results of both may be the most bizarre neurological symptoms and signs.

This has been a most sketchy account of these conditions but it is as much as space will allow.

### EFFECTS OF CARBON MONOXIDE

The effect of carbon monoxide could have been considered in the previous section without being out of place. We were dealing there with a reduced partial pressure of oxygen in the alveolar air leading to a deficient saturation of the hemoglobin and plasma with oxygen. In the present instance we will deal with a somewhat different process. The plasma of the arterial blood will contain a normal amount of dissolved oxygen but carbon monoxide has a greater affinity for hemoglobin than has oxygen. Therefore carbon monoxide hemoglobin will be formed and the combination of oxyhemoglobin prevented, in other words the CO usurps the place of the O<sub>2</sub>. In consequence the effects will be the same as if the partial pressure of oxygen were much reduced. The relative affinity of hemoglobin for these two gases is vastly different. It has an affinity for carbon monoxide 210 times greater than it has for oxygen. Therefore a mixture of gases containing 0.07 per cent of carbon monoxide, 20.93 per cent of oxygen, 0.03 per cent of carbon dioxide and 78.97 per cent of nitrogen would saturate the reduced hemoglobin equally as oxyhemoglobin and CO hemoglobin. From personal experience this produces moderate symptoms of anoxia after some time. The reason for the delay rests on the fact that the mixed venous blood contains only a relatively small amount of reduced hemoglobin and this will be saturated with CO but the oxyhemoglobin will remain undisturbed. As time passes the amount of CO hemoglobin will steadily mount until total equilibrium will be reached. There are several factors which hasten this. The most important is the amount of pulmonary ventilation, as when this increases the amount of CO supplied to the alveolar

air per minute increases. Physical exercise not only increases this but also creates a greater demand for oxyhemoglobin which is continuously decreasing in amount as its place is taken by CO hemoglobin.

**Symptoms**—The onset of symptoms in carbon monoxide poisoning is insidious, and the patient may be quite ignorant of his danger. When the concentration in the atmosphere rapidly increases, unconsciousness may develop with alarming rapidity. If it be less so headache and vertigo may be noticed with difficulty of vision and mental confusion. The degree of saturation of the hemoglobin with CO at which these symptoms appear varies considerably in different individuals and there is no doubt that those who are frequently exposed to carbon monoxide may develop a considerable tolerance or accommodation to high percentages of CO hemoglobin. This was particularly noticeable during World Wars I and II. Men serving in 'pill boxes' and in tanks were constantly exposed to a concentration which in time did not affect them but recruits frequently became unconscious. In those unaccustomed to it symptoms (see above) usually appear when the saturation reaches about 25 per cent and are soon followed by coma. The appearance of the patient is quite distinctive. Although unconscious his color is good and the skin is warm but in the terminal stages respiratory failure supervenes and if there is sufficient reduced hemoglobin present in the capillaries cyanosis will appear while if there is a vasomotor collapse the skin may be pale and clammy. During the coma tetanic or epileptiform convulsions frequently occur and there is relaxation of the sphincters.

Those who are constantly exposed to small amounts of the gas are supposed to develop a form of chronic poisoning characterized by headache, palpitation, dizziness, disturbance of gait, tremors, muscular twitchings and dyspepsia. There may be either a polycythemia or a hyperchromic anemia.

After a patient has been unconscious and has recovered from the effects of the gas there may be a residue of headache, lassitude, amnesia and various other nervous disturbances. He usually completely recovers in twenty-four to thirty-six hours except in the severe cases in which coma has been prolonged when dementia may result as the damage to the higher centers has been irreparable. Cerebral hemorrhage particularly in the basal ganglia has been reported with hemiplegia, monoplegia, paraesthesia and other prominent central nervous system disturbances. There is no evidence that this is due to a directly toxic effect of carbon monoxide but rather to extreme anoxia. Animals may be kept in a lethal concentration of CO but under a sufficiently high barometric pressure to charge the plasma with enough oxygen in solution to supply the tissues. In spite of practically complete saturation of the hemoglobin with CO these anatomical lesions do not occur.

**Diagnosis**—The diagnosis usually rests upon the coma and the history of exposure to carbon monoxide from some known cause such as illuminating gas, automobile exhaust in closed garages, in coal mines, from charcoal braziers in unventilated rooms, the imperfect explosion of munitions, slowly burning fires in lime or brick kilns and from all smoldering fires in which there is incomplete combustion due to lack of oxygen.

The *specific diagnosis* can be made by detecting carbon monoxide hemoglobin. Blood when drawn with oxalate has a carmine like appearance, which to the initiated is easily detected. It may be determined chemically by the pyrogallie tannic acid test. The most accurate method of estimating the amount present in the blood is by the photoelectric colorimeter devised by Evelyn. Spectroscopic methods may be employed, but these require expert knowledge, and with the usual instruments only large amounts can be detected with certainty.

**Prognosis**—The majority of patients recover without any after effects but if the blood has been saturated to 75 per cent, and the patient has been unconscious for more than half an hour, death usually occurs.

**Treatment**—The patient should be immediately removed from the environment of carbon monoxide and if the breathing has ceased, or is irregular with long periods of apnea, artificial respiration should be immediately instituted. Mechanical devices are to be condemned except the type of respirator devised by Drinker. These measures can be aided by the inhalation of 7 to 10 per cent carbon dioxide with oxygen until respirations are permanently established at a normal level. All patients do not respond equally well to the same concentrations of CO: some requiring higher percentages than others. It should be increased until deep respiratory movements are established. Intravenous injection of methylene blue has been advised in the treatment of this condition on the principle that it acts as a catalyst.

## CYANIDES

The use of cyanides for suicidal purposes has had a vogue from time to time. It produces almost instantaneous death. However, since the introduction of these compounds as vermifuges in the fumigation of ships dwellings etc. infested with cockroaches, bedbugs and other parasites it has become a more common danger due to the fact that a wider zone of environment may be polluted.

The action of the cyanides hydrocyanic acid cyanogen, etc. is to inhibit cellular oxidation immediately. The fumes are inhaled even though there may be an attempt at swallowing some of these compounds.

The victim is unaware of the presence of the fumes even in high concentration and instantly loses consciousness and dies. In greater dilution there are dizziness incoordination and rapid inability to perform muscular movements. As oxidation is arrested or at least decreased there is reduced consumption of oxygen and therefore no cyanosis even though respirations are arrested but there is a peculiar and distinctive pinkish violet tint to the skin and mucous membranes due to the presence of cyanhemoglobin. The various cyanides should only be used in treatment of hypertension with a thorough understanding of their action and dangers.

**Diagnosis**—The diagnosis rests upon the instantaneous action of the poison and the color of the skin supported by the probable pollution of the atmosphere or the presence of a container from which the poison may have been taken, as the suicide has not time nor opportunity to dispose of it.



**Prognosis**—The prognosis is always extremely serious. Death is often instantaneous. In milder intoxications recovery may occur.

**Treatment**—The treatment consists primarily in prevention by strict enforcement of the use of respirators by those entering places where cyanide fumigation has been done followed by thorough ventilation, particularly of pockets where free air currents do not have access. The fumigation of apartments and rooms in dwellings must be conducted with scrupulous care that the fumes cannot penetrate to occupied rooms by means of flues, dumb waiters, service elevators, laundry and garbage chutes, etc.

There is little specific active treatment that can be used. In borderline cases methylene blue has been advised on the principle of its acting as a catalyst. Experimental evidence would indicate that it may be of benefit when a minimal sublethal amount of cyanide has been present in the atmosphere. Its use has also been referred to in carbon monoxide poisoning.

### BENZENE POISONING

Benzene (Benzol  $C_6H_6$ ) poisoning is due to the inhalation of benzene fumes. This substance is a colorless volatile liquid the vapor of which is three times as heavy as air. It is without odor and nonirritating. It has been used principally as a solvent and was a favorite substance for cleaning clothes but has been largely discontinued because of its inflammability and toxic effects. It is still employed however in the extraction of fats and oils and is a constituent of rubber cement but even for this last use it has been largely replaced by latex, a liquid rubber. In chemical industry it plays an important part in the production of aniline dyes, phenol and picric acid and is also a constituent of many motor fuels. It will be seen therefore that it still has a wide use.

Its toxic effect is in direct proportion to its concentration in the atmosphere and the inhalation of fifteen parts in one thousand parts of air is rapidly fatal while the continued inhalation of one part in fifteen thousand will produce signs of chronic intoxication. All people are not equally susceptible but young women are supposed to be particularly so.

**Symptoms**—In acute poisoning occurring with high concentrations of the gas there is a rapid onset of dizziness, mental confusion, incoordination, coma and death. This may occur with great suddenness particularly in the benzene industry when men are exposed to a high concentration when cleaning or repairing machinery used in its manufacture or where it is employed as an adjunct in preparing other mixtures.

In chronic benzene poisoning the progress of the disease is much more insidious. The classical findings are described as a pan myelo toxicosis or aplastic anemia. The erythrocytes may be reduced to under a million. There is a leucopenia of less than one thousand resulting principally from a reduction of the granulocytes. There is also a pronounced thrombocytopenia. Therefore the symptoms are chiefly attributable to these severe blood changes and consist of weakness, dyspnea, palpitation, dizziness and great fatigue. Purpura and

hemorrhages from the mucous membranes are common, due to the thrombocytopenia. There may be melena, hematemesis, epistaxis, hematuria, hemoptysis and bleeding from the gums. Menorrhagia and metrorrhagia may be uncontrollable. If the patient continues to be exposed irreparable damage to the bone marrow occurs. More recent work has shown that this classical picture is only one of its manifestations. It is now quite clear that in chronic poisoning the opposite of this description may be encountered. There may be a polycythemia, leucocytosis, leucemic or leucemoid blood picture, eosinophilia, megalecytosis or microcytosis and immature marrow elements in the blood. The bone marrow histology may range from severe hypoplasia to hyperplasia, and the latter may be so extreme as to simulate tumors. In fact, acute myeloid leucemia and acute aleucemic leucemia have been reported. Early anemia and macrocytosis are looked upon as the first signs in chronic intoxication, and it is now clear that men are just as susceptible as women and are at present more frequently exposed in industries. Gant's test for decrease in the ratio of inorganic to organic sulphates is of great value but should be determined in the afternoon sample of urine.

**Diagnosis**—The diagnosis of the condition depends upon the appreciation of the persistent exposure to the gas. In the acute cases there is little doubt as to the diagnosis.

**Treatment**—The treatment consists principally in prevention. In industries where benzene is used, if there is a chance of its being present in high concentration proper respirators should be worn by the workmen. Young girls should not be allowed to engage in any occupation where there might be exposure to benzene fumes. In acute poisoning the victim should be removed to the open air and artificial respiration if necessary should be employed. In the more chronic cases the victim should not continue to be exposed, and repeated blood transfusions are indicated to tide the patient over the period of severe anemia and thrombocytopenia, in the hope that the bone marrow function may be re-established.

## OTHER GAS POISONS

The effects of the gases used in warfare have already been described. In domestic life after carbon monoxide the most common causes of gas poisoning are from mechanical refrigeration. These consist principally of methyl chloride which has a profound action upon the cerebral centers, the blood and kidneys, and sulphur dioxide and ammonia which are violent respiratory irritants. Nitric oxide was always a danger when inflammable x-ray films were in common use. It acts in a similar fashion to phosgene, having a direct action upon the alveolar epithelium and some hours after its inhalation acute suffocative pulmonary edema develops. Its action is most insidious. Hydrogen sulfide is a pronounced irritant to the eyes and may cause ulcerative keratitis. It also, in concentrated amounts, produces paralysis of the respiratory center and thus respiration may cease and the cardiac action continue. It sometimes acts as a pulmonary irritant leading to pulmonary edema or bronchopneumonia.

## MOTION SICKNESS

Motion sickness is a clinical syndrome consisting of vertigo, nausea and vomiting. Some people develop these symptoms when subjected to unusual motions such as in a boat, aeroplane, balloon, railway train, or closed motor car. It has been referred to in these special circumstances as 'seasickness,' 'air sickness' or 'car sickness.' An individual who suffers from seasickness does not necessarily suffer from car sickness, and also there are individual variations as to the different ships. A member of a crew may be quite free of all discomfort in a battleship but may be intensely seasick in a destroyer.

**Incidence**—There are few records which afford definite knowledge as to the frequency of seasickness but such as are available would indicate that severe cases occur in about 0.5 per cent of the passengers carried, and to a less degree among the crew. The relative immunity of the latter may be explained by the fact that adaptation often develops in those who take many sea voyages. Animals, such as dogs, horses, cows and sheep have been similarly affected, while hogs are thought to be immune. It is less frequent in infancy and in old age. It occurs in children but usually in a mild and transitory form.

**Etiology**—The exact cause of motion sickness has been the subject of much speculation and has been attributed to many factors. The balance of evidence would favor the conception that it is due to a disturbance, or increased sensibility of the labyrinthine apparatus as the symptoms can be closely simulated by syringing the ear with hot or cold water or by rotation (Barany test) and may also be produced in those susceptible by merry-go-rounds, swings and elevators. In the latter it is transitory. Any motion which simulates these rotary movements such as the corkscrew movement, rolling and pitching may produce these symptoms and signs. The secondary or contributing factors are found principally in the central nervous system and the eyes are probably the most important, particularly if the victim watches the horizon as it rises and falls. Added to this is the disturbance of deep muscle sense and some have claimed that it most usually occurs in those with a vagotonic constitution. Undoubtedly psychic factors are important and many people make up their minds that they are to be sick before the motion begins.

The symptoms closely simulate those of mountain sickness and motion sickness can be aggravated by the habit of unconsciously holding the breath with the motion. This is still further enhanced by watching the horizon.

**Symptoms**—The symptoms in this syndrome vary considerably. In the mildest cases there are a sense of tightness in the throat, salivation with frequent swallowing, and a gaseous sensation in the epigastrium. Nausea and headache soon follow. In appearance the victim is pale and there is a suggestion of cyanosis. The symptoms may not proceed further than this and accommodation is soon established. In more severe cases these symptoms are aggravated and the nausea culminates in explosive vomiting. There are then vertigo, incoordination and mental and physical lethargy. Some victims are flushed while in others the pallor and cyanotic tint become more pronounced. In the more severe forms prostration may become alarming. There

are sweating, cyanosis, thirst, and collapse. The skin is clammy, and the hands and feet are cold, the pulse is rapid and the body temperature subnormal. On account of the loss of gastric juice and the reduction in fluid intake the urine is scanty and highly colored, and may contain ketone bodies. There is often pronounced dehydration with blood concentration. The erythrocytes may number 8,000,000 to 9,000,000 per cmm. Finally there is vasomotor collapse and the patient may appear in a dying condition.

**Diagnosis**—The diagnosis is readily made. Other conditions are seldom confused with it, although the contrary occasionally occurs when a too hasty diagnosis of motion sickness may overlook some more serious constitutional condition. It assumed much prominence during the last war on account of its high incidence in the navy and air force and in the army in paratroopers and in amphibious operations.

**Prognosis**—Recovery usually occurs in three or four days, but in some the symptoms continue in a modified degree for a long time when the abnormal motion persists. Death does not occur from motion sickness but it may aggravate and render fatal other physical conditions. Recovery is assisted by will power and living in the open air, as in time adaptation to the new environment is accomplished and this is definitely delayed by the individual's having a fatalistic attitude toward the sickness.

**Treatment**—Prophylaxis would seem to be of considerable importance and this can be accomplished to some extent by careful attention to elimination. If a voyage begins with a period of inland water travel or if during the first few days the sea is smooth and there is little perceptible motion to the ship passengers frequently acquire their seasickness so to speak and are then immune. Those people who from experience are apprehensive of the condition during the first few days should spend as much time as possible in the open air and have their deck chairs placed in the middle of the ship. They should wear dark glasses, and at all costs avoid watching the horizon or looking at the sparkle of the sun on the water. The diet should be restricted to small amounts taken frequently and fluids should not be avoided but moderately restricted. Once seasickness has become established there are many remedies with variable reputations. Probably the best are those drugs which reduce the sensitivity of the labyrinthine apparatus and of these the bromides and barbiturates are the best. Hypnotics should be used to give the victim a night's sleep as rest is imperative. In severe cases with collapse the patient should be kept warm with blankets and hot water bottles. The fluid intake should be maintained being given in small amounts and in the most severe cases it may be necessary to administer 5 per cent glucose saline solution intravenously. Stimulants in the form of champagne, whisky and brandy are favorite remedies. If taken in sufficient quantities they would seem to produce a cure through their effect on the higher senses but most probably their chief effect is through suggestion. Recent research has made strides in the prevention of this condition. The drugs which have been found to be most effective are hyoscine, belladonna and barbiturates in various combinations. These are on the market under various trade names.

### SUBMERSION

This term is applied when an individual has been submerged in water for a short period and constitutes a form of suffocation which when death results is called drowning. The victim may be unconscious and show all the evidences of imminent death. The respirations may have ceased, or are infrequent and gasping. The pulse is rapid and may not be palpated. There are pallor and cyanosis, and the body surface is cold. This form of suffocation differs from others in that although there may be a small amount of water in the lungs there is much more in the stomach. Although the victim may appear dead when removed from the water energetic treatment should be immediately instituted. The clothing should be removed particularly over the upper part of the chest the patient should be laid out at length with the face downward but the head turned to one side and the tongue pulled forward. The rescuer should stand astride of the victim placing his hands under the abdomen the patient is lifted in an attempt to empty as much liquid as possible from the stomach. Artificial respiration by the Schriever method should then be immediately commenced. Rough handling should be avoided for fear of injury to the ribs and viscera. Artificial respiration should be kept up for several hours, particularly if there is at any time a suggestion of a spontaneous respiratory movement. If a respirator is available, the patient should be placed therein. The extremities should be massaged centrifugally only. Stimulants such as whisky strychnine caffeine camphor adrenalin etc are of little avail. If a respirator is used or even with artificial respiration the inhalation of 5 per cent CO<sub>2</sub> and 95 per cent oxygen is better than atmospheric air as it not only more readily overcomes the anoxemia but also acts as the best respiratory stimulant.

### EFFECTS OF RADIUM AND X RAY

It is not our purpose to deal with the local effects of irradiations whether from x ray or radium but rather to confine ourselves to a consideration of their more systemic reactions. In those susceptible to these irradiations a syndrome may develop which is known as 'radiation sickness or radiation toxemia'. There develop shortly after exposure general malaise weakness headache and prostration. There may also be nausea vomiting and diarrhea. These symptoms can be prevented to a great extent or ameliorated by the use of nicotinic acid. In addition to this immediate reaction anemia may develop in the course of several weeks if the exposures are continued. The erythrocyte count may be as low as 2 500 000 and the hemoglobin 40 to 50 per cent. More conspicuous is a leucopenia which occurs earlier and is more significant of deleterious systemic effects. If the leucocyte count falls below 3 000 radiations should be immediately discontinued. Although such blood changes develop with comparative rapidity in those who are particularly sensitive they may also occur in time in individuals who are not so afflicted but who are continuously exposed without protection to x ray or radium irradiations over a long period of time. This was particularly common in the early stages of the use of the

x ray and radium Since then accumulating knowledge has taught how to be protected from these effects In certain instances a severe and fatal anemia has occurred

A still more chronic effect is represented by the development of epithelioma in the skin of the hands which are most exposed In those working with radium who have survived the severe anemia, or in whom it did not occur osteogenic sarcoma has been a late manifestation of the toxic effect of these emanations In the cobalt mines of Schneeberg and the pitchblende mines of Joachimstal, in both of which the mine dust contains a considerable amount of radioactivity, bronchogenic carcinoma occurs in practically all miners who have been employed underground for more than a few years More local effects occurred in radium dial painters who pointed their brushes by sucking them This led to radium osteitis of the mandible or maxilla In addition to this there also occurred the general symptoms of anemia of the regenerative, pseudoaplastic or pernicious type, and bone lesions These were presumed to have resulted from the ingestion of minute quantities of radium over a period of time Similar symptoms to those described above have developed in those employed in the refining of radium or mesothorium in repairing radium needles plaques and containers and in the preparation of luminous paints The recent vogue of drinking radioactive waters is not without its dangers The natural or artificial waters which contain only gas emanations are probably harmless On the contrary waters made radioactive in various containers may possess quite dangerous qualities This has been a fad of recent years which could in no way be beneficial except through suggestion

There must also be mentioned the sterilizing effects on the gonads and ovaries This at times is used for therapeutic purposes but may also result from indiscrete exposure of those who are employing these agents

Radioactive substances whether taken into the body by inhalation or ingestion or directly through the skin are absorbed and taken up in a colloidal form by the reticulo endothelial system (see page 176) Eventually they are removed from these cells and find their way to the bones where they combine as carbonates and phosphates The alpha rays comprise over 90 per cent of these radiations and therefore there is a constant bombardment of the internal environment by these rays which finally exert their greatest effect upon the bone marrow where there is produced a hypoplastic condition particularly of the erythrocytic tissue and a great impairment in the production of granulocytes This bone marrow is finally replaced by fibroblasts In addition there is an osteitis which leads to decalcification fibrosis and softening which accounts for the frequent occurrence in these victims of spontaneous fractures

The development of the atomic bomb and the emphasis upon its terribly destructive power have created a new panic in the world The principal injuries from its use are divisible into two groups The first are due to the blast and are entirely traumatic after the same manner as explosive bombs The second are similar to those occurring on exposure to radium and x rays The systems chiefly affected are the hemopoietic dermal reproductive osseous etc Loss of hair has also been reported which is similar to that which results

from direct application of other radiations. Flash burns occur with considerable frequency due to the radiant heat. Which of these two groups is the more important has yet to be assessed. It has also the ultimate prognosis in the second group.

**Diagnosis**—The diagnosis rests upon the history of exposure, and the detection of the presence in the body of radioactive substances either during life or at postmortem. This may be accomplished in two ways, either by detecting radioactive deposits by a Geiger Muller counter or by collecting the exhaled air in special containers and having it examined by experts in radon analyses.

**Course and Prognosis**—The course and prognosis of harmful effects of irradiations from either  $\alpha$  or  $\beta$  radium or nuclear fission depend upon the amount absorbed over a period of time and it seems apparent to be more susceptible than others there may be considerable variation from case to case but any amount of radium over 2 micrograms is almost certain to produce grave bone lesions.

**Treatment**—The treatment is principally prophylactic, there being no specific treatment after certain amounts of radioactive substances have been absorbed. Attempts have been made to eliminate from the bones that which has been more recently deposited by using parathormone and a low calcium diet but this is of little avail in the majority of these patients, as they seek medical advice long after exposure. The anemia is best treated by liver extract but the results are only temporary. Surgical and dental procedures are often required to alleviate local bone lesions.

## EFFECT OF ELECTRIC SHOCK

Electric shock may be induced either by currents of high voltage or of comparatively low voltage as those used for domestic implements or from lightning.

**Low Voltage**—The standard voltage in domestic electric appliances is usually 110 to 120 volts and is considered to be harmless. But if contact is made when the hands or the body are wet or are immersed in water there may be a fatal result. This not uncommonly occurs when an individual in a bathtub attempts to turn off an electric light or to move electric implements such as irons, fans or heaters.

**High Voltage**—When an individual comes in contact with electrical currents of high voltage such as stepping upon a broken high tension wire or grasping one in the hands or by leaning against one as sometimes occurs in those employed in line work for electrical companies there is instantaneous contraction of all the muscles. If the hand has grasped the wire it cannot be released and the individual is said to be "frozen" to it as long as the current continues. Severe burns are produced in this manner which may completely char even the bones (electrocution).

**Effects of Lightning**—The number of volts which are contained in a lightning bolt must be enormous probably numbering millions and thousands of amperes. Death when it occurs is probably instantaneous although it is variously estimated that about one half recover.

The principal symptom from electric shock is coma with cessation of respiration, although the heart continues to beat until it ceases from asphyxia. In the nonfatal cases there are collapse, tremors, convulsions and during recovery vomiting and photophobia. Local burns, ecchymoses, and abrasions are almost constantly found in people struck by lightning.

The principal causes of death are ventricular fibrillation and respiratory arrest. Others suggested have been prolonged muscular tetany causing asphyxia, the delayed effects of burns, and tissue coagulation from intense heat production. If the ventricular fibrillation is permanent, death is certain to occur. In most cases however, prolonged apnea is more prominent than cardiac arrest.

**Treatment**—The individual must be released by *shutting off the current* as soon as possible, *not* by being pulled away, as this will probably add another victim. Artificial respiration should be immediately instituted. This must be maintained for many hours, and is best carried out by the rescue crews of public utility organizations. These men are skilled in the performance of the Schaefer method and have resuscitated victims up to nine hours after the shock has been induced. The use of carbon dioxide in these cases has been of little or no benefit nor have the so called cardiac and respiratory stimulants. In fact valuable time may be wasted in delaying the institution of artificial respiration while these are being procured, or by interrupting it to administer them.

### References

- Barcroft J Binger, C A Bock, A V et al. Observations Upon the Effects of High Altitude on the Physiological Processes of the Human Body, Carried Out in the Peruvian Andes Chiefly at Cerro de Pasco Phil Tr Roy Soc, London, B 211 351, 1923
- Bock A V and Dill D B. Results of Some Physiological Reactions to High External Temperature. New England J Med 206 442 1932
- Boothby W M and Lovelace W R II. Oxygen in Aviation J Aviation Med 9 119 1139
- Boycott A E Damant G C C and Haldane J S. The Prevention of Compressed Air Mines J Hyg 8 342 1903
- Dill D B and Hall F C. Gas Exchange in the Lung at High Altitudes J Aeronaut Sc 2 220 1942
- End E. Rapid Decompression Following Inhalation of Helium Oxygen Mixtures Under Pressure Am J Physiol 120 111 1937
- Gettler A O and Mattice M R. The Normal Carbon Monoxide Content of the Blood J A M A 100 91 1933
- Haldane J S. Respiration New Haven 1922 Yale University Press
- Haldane J S. Carbon Monoxide as a Tissue Poison Biochem J 21 1068 1927
- Hamilton A. Benzene (benzol) Poisoning Arch Path 11 434 and 601 1911
- Hamilton A. Industrial Poisons in the United States New York 1922, Macmillan Co
- Hancock W Whitehouse A G H and Haldane J S. The Loss of Water and Salt Through Skin Proc Roy Soc 3 105 43 1929
- Hill L. Cussion Sickness London 1922 Edward Arnold & Co
- Hoff H I and Nahum L H. Nature of Ventricular Fibrillation Following Electric Shock and Its Prevention by Acetyl Methyl Choline Chloride Am J Physiol 110 615 1935
- Hooker D R. On the Recovery of the Heart in Electric Shock, Am J Physiol 91 95 1929 30



- Hurtado A Blood Observations on Indian Natives of Ieruvian Andes *Am J Physiol* 100 487, 1932
- Jaffe H H Electropathology *Arch Path* 5 837, 1928
- Jones, R R, Crosson, J W, Griffith, I F, Sayers, R R, Schrenk, H H, and Levy, E Administration of Pure Oxygen to Compressed Air Workers During Decompression Prevention of Occurrence of Severe Compressed Air Illness, *J Indust Hyg & Toxicol* 22 4, 1940
- McCord, C I Benzol Poisoning, Cincinnati, 1931, Industrial Health Conservancy Laboratories
- McCord C I Occupation and Health, Int Lab Off, Geneva 1 229 1930
- McCord C I and Ferenbaugh, T L Fatigue in Soldiers Due to Chloride Losses *Mil Surgeon* 69 608, 1931 Bibliography
- MacLachlan W Electric Shock *J Indust Hyg* 12 201, 1920
- Martland H H Occupational Poisoning in Manufacture of Luminous Water Dials, *J A M A* 92 466 and 552, 1929
- Martland H S The Occurrence of Malignancy in Radio Active Persons *Am J Cancer* 15 243, 1931
- Martland H H Colon I and Knaf J P Some Unrecognized Dangers in the Use and Handling of Radio Active Substances With Special Reference to the Storage of Insoluble Products of Radium and Mesothorium in the Reticuloendothelial System *J A M A* 111 169 1925
- Morrison L R, Week\*, W and Cobb S Histopathology of Different Types of Electric Shock on Mammalian Brain *J Indust Hyg* 12 224 1930
- Morton T C St. C. The Etiology and Treatment of Heat Exhaustion and Heat Hyperpyrexia *Proc Roy Soc Med* 25 1-61, 1932
- Little G C, Johnson H I and Consolazio F C Work in the Heat as Affected by Intake of Water Salt and Glucose *Am J Physiol* 142 203 1944
- Polak I B and Adams, B H Traumatic Air Embolism in Submarine Escape Training *U S Nav Med Bull* 30 16, 192
- Sayers, R R and Davenport H J Review of Literature on the Physiological Effects of Abnormal Temperatures and Humidity *Pub Health Rep* 42 933, 1927 Reprint No 1153 U S P H S Washington Very extensive bibliography
- Sayers R R, Yant W P and Hildebrand J H Possibilities in the Use of Helium Oxygen Mixtures as a Mitigation of Caisson Disease *U S Bureau of Mines Washington*, 192 Reports of Investigations No 2670
- Schlundt H, Barker H. H and Flinn F H The Detection and Estimation of Radium and Mesothorium in Living Persons *Am J Roentgenol* 21 345 1929
- Schneider E C Physiological Effects of Altitude *Physiol Rev* 1 631 1921
- Schneider, E C The Vital Capacity of the Lungs at Low Barometric Pressure, *Am. J Physiol* 100 4-6 1932
- Smyth H F Toxicity of Certain Benzene Derivatives and Related Compounds *J Indust Hyg* 13 87 1931
- Talbot J H Heat Cramp *Medicine* 14 3 1935
- Thorne I J Caisson Disease A Study Based on 500 Cases Observed at the Queens Midtown Tunnel Project 1938 *J A M A* 117 58, 1941
- Wiggers C J Ventricular Fibrillation Caused by Electric Shock *Am Heart J* 5 351 1930

## CHAPTER XXIII

### DISEASES DUE TO CHEMICALS AND DRUGS

#### INTRODUCTION

To accomplish a complete review of the toxic effects of all chemicals and drugs would rightfully require a treatise on toxicology, which is quite out of place in this volume. There are, however, a number of chemicals and drugs which on account of their common use either in therapeutics, or as contaminants of food and water or because they are used for pernicious purposes and produce a habit will be considered in this section. As they affect the individual by direct ingestion or injection, and not through change of the external environment, they are not strictly comparable with those dealt with in the preceding chapter.

#### ETHYL ALCOHOL

Alcohol has been used as a stimulant or a narcotic since the earliest historical records, and has been produced from many substances by fermentation. Symptoms of its toxicity usually appear when the blood contains 0.1 per cent and if the concentration be increased to 0.5 per cent the result may be fatal. There is, however, a great variation in the susceptibility of different people to its toxic action and this is usually decreased in direct proportion to the duration of the habit. In many people its use results in a 'habit' and in these definite withdrawal symptoms are apparent when its consumption is discontinued. The amount of alcohol consumed over a period of time does not in all individuals produce the same symptoms or the same degree of intoxication. Therefore the results of its ingestion are not necessarily always the same.

#### Acute Alcoholism

A small amount of alcohol whether in the form of spirits, wines or brewed liquors produces exhilaration and a general feeling of well being. It decreases the sense of fatigue and gives to the individual an increased jollity and the idea of enhanced capacity for accomplishment and consequent importance but with larger amounts, particularly if taken in a concentrated form this stage is rapidly passed and the individual enters a phase of mental confusion, loss of memory and change of personality some individuals becoming noisy and boisterous and others morose and sullen. There is muscular incoordination. In some individuals this affects all extremities but in others chiefly the legs, and they may appear apparently sober until they attempt to walk. The skin is flushed and moist, while the pulse is full and accelerated respirations are slow and deep. If sufficient alcohol has been taken these symptoms may progress to somnolence unconsciousness and coma. The pupils are dilated and the body temperature lowered. These are important contraindications to its use when an individual is exposed to intense cold. This stage may be followed by vasomotor collapse and occasionally death.

Such acute forms of alcohol poisoning are usually rapidly recovered from, but their recognition is important in the differentiation of uremia apoplexy, fracture of the skull and other causes of coma. The detection of the odor of alcohol on the breath should not be taken as an absolute diagnostic sign to the exclusion of other possibilities as an individual may have taken some spirits before an attack of uremia or apoplexy and there would be only a coincident relationship. On the other hand through incoordination the individual may have fallen and fractured the skull or have been assaulted in a brawl.

**Treatment**—The treatment of these acute cases is directed toward the removal of the stomach contents. Although vomiting is frequent this should be supplemented by gastric lavage or an injection of apomorphine. After the stomach is empty food of a liquid high caloric character should be introduced and the patient left alone in warm surroundings until the effect of the intoxication disappears.

### Chronic Alcoholism

This takes on a variety of forms. Its principal effect is upon the nervous system although it may have an aggravating effect upon lesions of the cardiovascular system and liver. There is no absolute proof that it can of itself initiate anatomical changes in these latter organs. The principal evidence of chronic alcoholism is a depreciation of the mentality and personality of the individual. Association of ideas memory initiative reasoning and judgment are all impaired while their emotional responses are explosive. All these symptoms may be evident during intermittent periods of subacute alcoholism but as the practice of imbibing becomes continuous so may these changes become permanent. After the individual has been without alcohol for some hours, as for instance after a night's sleep there is an intense craving for it. There are pains in the limbs unsteadiness and tremor sweating and general depression. A fair estimate of the degree of chronic alcoholism may be obtained by ascertaining how much alcohol the individual requires in the morning (often before breakfast) to prepare him for the day's work.

There are a number of phases of chronic alcoholism to which particular names have been given the principal ones are the following

### Alcoholic Trance or Automatism

This occurs in highly neurotic or psychopathic people and has also been associated with epilepsy heat stroke and cerebral injuries. In the majority of people in whom this occurs a small amount of alcohol only is necessary to induce it. There is an entire lack of orientation and they enter into a condition of trance in which they may do sensible things, but on the other hand may commit crimes or behave in a most absurd manner being quite unconscious of their actions.

### Delirium Tremens

This is a state of acute delirium usually preceded by certain premonitory signs such as euphoria excitement and restlessness. It is seldom seen in wine and beer drinkers, being most commonly found in those who are habitual

## CHAPTER XXIII

# DISEASES DUE TO CHEMICALS AND DRUGS

### INTRODUCTION

To accomplish a complete review of the toxic effects of all chemicals and drugs would rightfully require a treatise on toxicology which is quite out of place in this volume. There are, however, a number of chemicals and drugs which on account of their common use either in therapeutics or as contaminants of food and water or because they are used for pernicious purposes and produce a habit will be considered in this section. As they affect the individual by direct ingestion or injection, and not through change of the external environment, they are not strictly comparable with those dealt with in the preceding chapter.

### ETHYL ALCOHOL

Alcohol has been used as a stimulant or a narcotic since the earliest historical records and has been produced from many substances by fermentation. Symptoms of its toxicity usually appear when the blood contains 0.1 per cent, and if the concentration be increased to 0.5 per cent the result may be fatal. There is, however, a great variation in the susceptibility of different people to its toxic action and this is usually decreased in direct proportion to the duration of the habit. In many people its use results in a 'habit' and in these definite withdrawal symptoms are apparent when its consumption is discontinued. The amount of alcohol consumed over a period of time does not in all individuals produce the same symptoms or the same degree of intoxication. Therefore the results of its ingestion are not necessarily always the same.

### Acute Alcoholism

A small amount of alcohol whether in the form of spirits, wines or brewed liquors produces exhilaration and a general feeling of well being. It decreases the sense of fatigue and gives to the individual an increased glibity and the idea of enhanced capacity for accomplishment and consequent importance, but with larger amounts, particularly if taken in a concentrated form this stage is rapidly passed and the individual enters a phase of mental confusion, loss of memory and change of personality, some individuals becoming noisy and boisterous and others morose and sullen. There is muscular incoordination. In some individuals this affects all extremities but in others chiefly the legs and they may appear apparently sober until they attempt to walk. The skin is flushed and moist while the pulse is full and accelerated, respirations are slow and deep. If sufficient alcohol has been taken these symptoms may progress to somnolence, unconsciousness and coma. The pupils are dilated and the body temperature lowered. These are important contraindications to its use when an individual is exposed to intense cold. This stage may be followed by vasomotor collapse and occasionally death.

pletely oriented as to his surroundings, but the hallucinations continue. Recovery is usual but the more severe cases may progress into a chronic delirium or dementia, or what is known as 'Korsakoff's syndrome or psychosis'.

**Treatment**—The treatment is the same as for delirium tremens but as the condition lasts longer it is imperative to maintain the nutrition, and this is best accomplished through a high carbohydrate diet rich in vitamins.

### Wet Brain

In prolonged chronic alcoholism, usually with a record of a number of attacks of delirium tremens, or a recent severe trauma, the patients sink into a state of semicoma with muttering delirium. They lie flat on their back staring at the ceiling, and hold their arms upward before them as though they were trying to grasp something just beyond their reach, and this position sometimes simulates catalepsy. The arms however, are not immobile but are constantly in a state of tremor, and there is a continuous mumbling of incoherent words. They remain completely indifferent to their surroundings or their physical state. When given food they make no attempt at swallowing and are aroused with the greatest difficulty. There are tachycardia and low pyrexia. This state may last for weeks and the patient may become dehydrated, emaciated, and pass into a state of collapse. If and when recovery occurs, the convalescence is prolonged extending into months and there may be a permanent residue of mental depreciation or dementia.

**Treatment**—The treatment consists principally in nursing and the maintenance of nutrition. This is difficult on account of the patient's inability or lack of attempts to swallow and aspiration of food frequently leads to pneumonia which is practically always fatal. It may be necessary to feed the victim either by a nasal tube or stomach tube and large quantities of water should be given either by mouth or by rectum through a Murphy drip. Intravenous injections of 50 per cent glucose or 25 per cent sucrose are of great assistance in reducing the cerebral and meningeal edema.

### Korsakoff's Syndrome or Psychosis

Korsakoff's syndrome or psychosis is a combination of a delirium and polyneuritis. There are profound personality changes the individual often being either maniacal or melancholic. The attention may be fixed for a few moments but quickly wanders. There may be loss of memory with falsification and the mental attitude is childish or even idiotic.

The anatomical changes in this condition have been identified as a peripheral neuritis and a degeneration of the cerebral cortical cells. There has been some doubt expressed as to whether it is altogether due to alcoholism but rather that these lesions are a result of avitaminosis especially vitamin B complex. There is probably a combination of these causes. The neuritis may involve all four extremities and the cranial nerves and may affect both motor and sensory functions. The pupils are frequently unequal or contracted and sometimes have the features of the Argyll Robertson pupil.

users of whisky, gin, brandy, and other spirituous liquors. It may develop during a period of intense and persistent alcoholism or be precipitated in more moderate imbibers who have suffered a severe shock, accident, or acute infection, such as sunstroke, fractures, operations, traumatic injuries and infections such as influenza, pneumonia, or erysipelas.

**Symptoms**—The symptoms are more violent during the night than during the day, the most prominent being hallucinations of sight. These may be concerned with the ordinary articles or animals of a household, or the individual's daily round of duties. On the other hand they may take the form of terrifying animals of bizarre and unreal shapes and colors. The individual has little or no conception of his surroundings, and fails to recognize familiar objects or people. The memory is completely lost. Some remain subdued and terrified while others are violent and noisy and try to escape from their unreal environment. There are incoordination of the arms and legs, and a constant trembling of the limbs, body and tongue, which interfere not only with coordinated action but also with speech.

The constitutional reactions are sometimes pronounced. There may be pyrexia, tachycardia, low blood pressure, sweating, complete anorexia and sleeplessness. The attack usually continues in proportion to its intensity for a week to ten days and terminates almost by crisis when the patient falls into a deep sleep and awakens after ten to twenty hours in complete ignorance of what has happened. Hallucinations have disappeared but the mental processes are sluggish and uncertain.

**Prognosis**—The prognosis is usually good unless there is an intercurrent infection or the individual has been debilitated from lack of nourishment and neglect.

**Treatment**—The treatment consists of careful watching and absolute rest in bed. All means should be taken to prevent struggling and full doses of sedatives such as bromides, chloral, paraldehyde and barbiturates may be given. External hydrotherapy for the pyrexia and nervous agitation should be employed while if the temperature is subnormal warm baths with friction are beneficial. A concentrated caloric and liquid diet should be given with large amounts of vitamin B complex by mouth and parenterally when possible. Any coincident lesion should be suitably treated.

### Acute Alcoholic Hallucinosis

Closely allied to delirium tremens there is a condition called *acute alcoholic hallucinosis* which differs from it in that the hallucinations are more likely to be auditory than visual and it is more apt to occur in young persons. It may also closely simulate acute paranoia or persecutory insanity. Voices and commands or upbraidings and accusations are heard which drive the patient into a state of terror and they often attempt suicide to escape from them. The hallucinations are often attributed to people in attendance or the family and the patient is suspicious that food or drugs are poisonous.

**Course**—The course is longer than in delirium tremens the attacks may last up to six or eight weeks. During this time the patient may be com-

there may be complete loss of sight due to retrobulbar neuritis. There may be some improvement in vision for a while, but eventually there is permanent blindness.

**Treatment**—The treatment is directed toward removal of the alcohol from the stomach by gastric lavage and combating the acidosis by alkalis. The latter does not influence the ultimate course of the disease, and only helps to correct this single condition.

## GINGER PARALYSIS

Associated with prohibition there appeared during 1930 a group of cases of flaccid paralysis of the arms and legs. This was traced to drinking an adulterated fluid extract of Jamaica ginger. The neuritis was at first considered to be due to alcohol but it was later shown by Smith and Elvove that it was caused by an adulterant in the ginger which was a phenol ester having the properties of triorthocresylphosphate.

## OPIUM

Opium has been used by the laity apart from its medicinal indications for centuries. In India and China this is customary among the general population and although it is a habit forming drug it is on record that among Orientals who use it in moderation they may do so for many years without any important deleterious effects. With such people it is treated as a social custom rather than a vicious one and is comparable to the moderate use of alcohol in the occidental countries. It is true that these people have great difficulty in giving up its use but there is no indication that they are required to increase their daily allowance. Although it may be stated that they develop a habit for its use this cannot be looked upon as a very vicious one.

On the other hand the use of morphine and heroin (and codeine as a substitute in times when neither of these can be obtained) leads to a most pernicious and progressive habit. The addiction to morphine is frequently initiated by prescribing it indiscreetly for severe painful conditions such as trigeminal and other severe neuralgias, tabetic crises, etc. If either morphine or heroin is to be prescribed the patient should be ignorant of their character particularly in those who are neurotic or emotionally unbalanced as they soon find that it gives them relief from their physical and mental agitations and an opportunity to forget the unpleasant past. The heroin habit on the other hand is more usually acquired from social contact. It is started in ignorance particularly among the young and as will be seen, leads to both social and physical degradation. Codeine is a much less active drug and is taken with greater difficulty as the amounts required to produce an effect by mouth are large. It cannot be obtained usually in a form for hypodermic use and therefore it is injected intravenously. It is seldom that a codeine habit is so by desire but rather from necessity.

Morphine may be taken by mouth but more usually hypodermically while heroin is taken by mouth or as a snuff like cocaine. The most common method of using opium is by smoking it. This is the favorite method of the Orientals.

**Course**—The course is prolonged and the outlook doubtful for complete recovery. Their emotional reactions remain unstable, and the slightest amount of alcohol produces an acute recurrence of symptoms.

**Treatment**—The only treatment is rest, good nursing, generous diet, vitamin B complex intravenously or intramuscularly and time.

### Peripheral Neuritis

A peripheral neuritis may occur in chronic alcoholics, particularly women. It is characterized by a gradual onset with pains in the limbs and subjective changes of sensation, with progressive weakness to paralysis. It first affects the extensors of the legs and feet and then later the arms and hands leading to wrist drop and foot drop. There are exquisite tenderness over the muscles, stasis and often swelling of the extremities. There is now a body of opinion which attributes this neuritis in large part to vitamin B deficiency. This may be absolute from dietary lack or relative through the fact that in intoxications like alcohol there is required a much larger intake of the vitamin to be effective. Recovery is usually complete but in severe vitaminosis may take many months to years. The treatment should be directed to prohibition of alcohol and concentrated vitamin B by mouth and parenterally. In the meantime muscle tone and nutrition must be maintained by physiotherapy.

### Dipsomania

In some people, particularly those with a family history of alcoholism, there may be periodic bouts of intoxication. These individuals go through life in definite cycles of sobriety and drunkenness. For months they may not take any alcohol nor have a desire, but for some unknown reason an irresistible craving for it develops and then they go on a bout for an indefinite period or this may be precipitated by a single drink. In time this craving subsides, often terminating in an attack of delirium tremens and when recovered they loathe and detest both alcohol and themselves and enter a period of total abstinence. These bouts closely simulate the cycles of manic depressive insanity, the alcohol representing the period of depression.

### METHYL ALCOHOL

Methyl alcohol differs from ethyl alcohol in that it is not completely oxidized in the body, but formic acid is formed which has a specific toxic effect. This intoxication may be brought about either from drinking methyl alcohol or ethyl alcohol adulterated with wood alcohol or in some occupations the fumes may be inhaled in sufficient concentration as to produce an intoxication closely resembling that of ethyl alcohol poisoning, but the symptoms are more unpleasant and consist of nausea, vomiting, abdominal cramps, diarrhea, and dizziness. Formic acid produces an intense acidosis leading to hyperpnea and dyspnea which brings about a low CO content of the alveolar air and also a low CO combining power. There are cyanosis and intense thirst. Difficulty of vision is at first attributed to the intoxication but in a few hours



Opium and its derivatives do not produce any demonstrable anatomical effects except those which result from malnutrition, lack of sleep, and personal neglect. It is true that habitues are often pale and there is constant sweating, the pulse and respirations are slow, the pupils are dilated except when under the action of the drug when they are contracted. There are usually absence of deep reflexes, paresthesia and hyperesthesia of the feet which may prevent walking.

The most pernicious habit is that due to heroin. Morphine is next and finally opium. This is due not only to the ease with which heroin can be taken but also to the action inherent in its intoxication. The gravity of the situation is also enhanced by the fact that the habit assumed almost the proportions of an epidemic among the younger generation during the 1930's. This however has now considerably subsided due to the difficulty of obtaining the drug through the incessant vigilance of narcotic control. In some countries its use is now prohibited even for medicinal purposes.

**Course**—The course of the habit is determined by a number of factors. If there is not the desire on the part of the individual to be cured, all attempts to this end are of little avail. Although this may be brought about through force it is usual when the victim has been released from constraint that he returns to the habit. On the other hand if there is a sincere desire to be rid of this awful curse, a return is less likely. This is particularly the case in morphine habitues who have acquired the habit through its continued administration to relieve pain when this has ceased a patient may often be permanently cured. However through the period in which the drug has been taken there has been a depreciation of moral sense and will power which is not the best equipment to protect from temptation an individual who has once known relief of unpleasant conditions by its use. It has been stated by those competent to judge, that a heroin addict is seldom permanently cured. The majority of these habitues are perverts and take a devilish delight in contaminating others. The mental depreciation is more pronounced than with morphine.

The effect of these drugs upon the patient's general condition renders him more liable to intercurrent infections and in this way his longevity is affected.

**Treatment**—The treatment of the addiction can be carried out satisfactorily only in an institution. They should be isolated and placed in competent hands. Before the withdrawal of the drug is begun their general nutrition should be satisfactory. If there is emaciation a high caloric diet is given for some days and the patient assured periods of rest and sleep. During this time the minimal amount of the drug necessary to relieve symptoms can be ascertained but it must be remembered that these addicts are habitual liars and may have secreted a supply in the most unlooked for places. Even with the removal of all their clothing small vials of the drug may be secreted in the mouth, the nose and even the rectum and vagina. This is to be suspected in those who are being subjected to a cure by force.

There have been a number of methods proposed for the withdrawal of the drug many of which were not without their dangers. It is the generally

and at one time was much more common among Occidentals than at present as they are now more addicted to morphine and heroin

There are considerable differences of susceptibility between people. Some beginners are affected by very small amounts, but all rapidly acquire a tolerance which requires increasing amounts to be taken to produce the desired effects. There are a few individuals who can restrict their daily allowance without any uncomfortable symptoms

**Symptoms**—*Acute opium poisoning* is characterized by coma, sweating, pinpoint pupils and slow respiratory rhythm which may be reduced to two to six per minute. This is the picture of the full toxic effect of this drug, the outstanding feature being resistance of the respiratory center to normal stimulation. Therefore, it is best treated by inhalations of 7 to 10 per cent carbon dioxide with pure oxygen. It may be necessary to place the victim in a respirator, and while this is in operation to have him inhale this gas mixture. The stomach should be washed out as morphine is secreted by the stomach, and large amounts of coffee given as it is up to a point, a physiologic antidote. On the other hand the general depressive effect upon the central nervous system can be counteracted by the use of picrotoxin given in 5 to 10 mg. doses every half hour until there are muscular twitchings or spontaneous response to painful stimuli. This treatment should be maintained until there is some evidence of the toxic effects subsiding. This may take many hours. Cardiac arrest is the final indication of death.

The symptoms arising from continuous use of opium or its derivatives are roughly divisible into two phases. With the first few doses there is a pronounced and pleasant euphoria which removes the victim to a high state of pleasant exhilaration which is almost beatific. It is to reacquire this that the drug is repeated and this would be particularly desirable when the individual is suffering intense pain. The effect of a single dose usually lasts about three to six hours and with the return of the pain there is naturally an urgent desire for its repetition. If relief of pain was not the original reason for its use it may be repeated merely to recapture the former exhilaration. If this is continued at frequent intervals over a period the pleasurable sensations disappear and are replaced by what are known as 'withdrawal symptoms' which chiefly consist of mental depression, physical lassitude, nausea and dyspepsia. There is in addition an intense desire for the drug which is out of proportion to the physical symptoms complained of. Up to this time there may be no outward or manifest sign as in alcoholism that the person is a victim of this habit but in time definite changes in personality appear. They become selfish, inconsiderate, indifferent to their responsibilities, slovenly in personal appearance, behavior and dress, irritable, suspicious and prone to outbursts of anger. They have insomnia or fitful sleep disturbed by dreams. They lose their initiative and ambition and being conscious of this leads to self condemnation, remorse and inferiority, but at the same time they are resentful of criticism or advice. The more pronounced cases have hallucinations of sight and hearing, loss of memory, anorexia, pruritis, nausea and constipation.

Opium and its derivatives do not produce any demonstrable anatomical effects except those which result from malnutrition, lack of sleep and personal neglect. It is true that habitues are often pale, and there is constant sweating, the pulse and respirations are slow the pupils are dilated except when under the action of the drug when they are contracted. There are usually absence of deep reflexes, paresthesia and hyperesthesia of the feet which may prevent walking.

The most pernicious habit is that due to heroin. Morphine is next and finally opium. This is due not only to the ease with which heroin can be taken but also to the action inherent in its intoxication. The gravity of the situation is also enhanced by the fact that the habit assumed almost the proportions of an epidemic among the younger generation during the 1930's. This however has now considerably subsided due to the difficulty of obtaining the drug through the incessant vigilance of narcotic control. In some countries its use is now prohibited even for medicinal purposes.

**Course**—The course of the habit is determined by a number of factors. If there is not the desire on the part of the individual to be cured, all attempts to this end are of little avail. Although this may be brought about through force it is usual when the victim has been released from constraint that he returns to the habit. On the other hand if there is a sincere desire to be rid of this awful curse a return is less likely. This is particularly the case in morphine habitues who have acquired the habit through its continued administration to relieve pain when this has ceased a patient may often be permanently cured. However through the period in which the drug has been taken there has been a depreciation of moral sense and will power which is not the best equipment to protect from temptation an individual who has once known relief of unpleasant conditions by its use. It has been stated, by those competent to judge that a heroin addict is seldom permanently cured. The majority of these habitues are perverts and take a devilish delight in contaminating others. The mental depreciation is more pronounced than with morphine.

The effect of these drugs upon the patient's general condition renders him more liable to intercurrent infections and in this way his longevity is affected.

**Treatment**—The treatment of the addiction can be carried out satisfactorily only in an institution. They should be isolated and placed in competent hands. Before the withdrawal of the drug is begun their general nutrition should be satisfactory. If there is emaciation a high caloric diet is given for some days and the patient assured periods of rest and sleep. During this time the minimal amount of the drug necessary to relieve symptoms can be ascertained but it must be remembered that these addicts are habitual liars and may have secreted a supply in the most unlooked for places. Even with the removal of all their clothing small vials of the drug may be secreted in the mouth the nose and even the rectum and vagina. This is to be suspected in those who are being subjected to a cure by force.

There have been a number of methods proposed for the withdrawal of the drug many of which were not without their dangers. It is the generally

accepted custom now to proceed with the withdrawal in an orderly fashion. When the minimal amount has been ascertained, this is reduced by  $\frac{1}{10}$  per day, so that at the end of ten days the total withdrawal is accomplished. During this period the patient exhibits the usual withdrawal symptoms. There are first yawning, restlessness, trembling, abdominal cramps, diarrhea and pruritus in the joints and muscles. The patients are frequently violent, even maniacal and may require physical restraint. They may refuse food and liquids, and rapidly lose weight and become dehydrated with concentration of the blood. This condition should be prevented at all costs. Some advise the use of codeine as a substitute during this period, increasing the amount from  $\frac{1}{2}$  grain (0.03 gram) every four hours on the first day up to 5 grains (0.3 gram) every four hours by the fifth day. This is continued for the rest of the period and for five days after complete withdrawal. The amount of codeine is then rapidly reduced until at the end of five days no drugs are being used. It must not be forgotten, however, that codeine is used by habitues of both morphine and heroin to tide them over a period when these drugs are not available and with the increasing difficulty of obtaining heroin codeine habitues are becoming more numerous. In most places they have no difficulty in obtaining the drug but it cannot be obtained readily in a form suitable for hypodermic use. They, however, become very skillful in its intravenous administration and if necessary will go to all lengths to procure it.

### COCAINE

The use of cocaine was more popular some decades ago than it is at present. Its principal effects are to relieve pain and give a sense of mental and physical exhilaration and increased power. Immediately after taking the drug the conversation of the addicts is glib and inconsequential but as its effect wears off they become restless, have insomnia, pains in the limbs, tremors and choreiform movements. They become suspicious, unreasonable and fearsome, particularly on account of auditory, visual and tactile hallucinations. They complain of creeping sensations in the skin as if they were being eaten by insects. They are irritable and quarrelsome and acquire slovenly habits, a neglect of personal hygiene and an indifference to food. This is followed by pallor, emaciation and general muscular debility.

In a certain number of cases where the habit has been present for a long period, acute delirium or insanity may occur. All the delusions and hallucinations are exaggerated and they may become extremely violent. Upon withdrawal of the drug the hallucinations quickly disappear but the delusions remain. The course of this acute insanity usually covers a few weeks but there is often permanent mental depreciation.

Cocaine like morphine but unlike alcohol may not give rise to symptoms which can be recognized in the early stages of the habit but as it progresses the rapid changes from exhilaration to depression, the changes in personality, neglect of the person and clothing should always arouse suspicion but they are so secretive and such inveterate liars that it may be difficult to detect them in the act, particularly as they seek solitude to enjoy its effects. The presence of false ideas of persecution is most significant.

It is easier to cure a cocaine habitue than one addicted to morphine or heroin, but on the other hand it is more difficult for these victims to remain cured.

**Treatment**—The treatment is similar to that outlined for morphine. They are less liable in the early stages of withdrawal to acute maniacal outbursts and when this does occur, it arouses suspicion that morphine or heroin has been used with the cocaine.

### **Cannabis Indica**

**Synonyms**—Indian hemp, Hashish, Marijuana

**Symptoms**—This drug has been used almost exclusively in Africa and eastern countries as a stimulant and intoxicant for centuries. In recent years it has acquired a vogue in America until at present it is used extensively. The drug is contained in the dried flowering tops of the female plants of *Cannabis sativa*, an herb of the family Moraceae. When grown in tropical and subtropical countries it produces a larger amount of resin. The highly active plant grown in India differed only in this regard to other hems, although at one time it was considered a different species hence the name *Cannabis indica*. It can be grown with great ease in North America in fact may be classed as a weed.

In eastern countries the resinous exudation is employed as a beverage a sweetmeat and is also smoked but in America it is used in the form of a cigarette (called 'reefers') and the fumes are inhaled.

The acute symptoms are exhilaration, laughter, singing and the response to rhythm allows of a more rapid tempo and improvisation becomes easy even for the mediocre musician. Time and space become diminutive and much can be accomplished in a seemingly short period. It does not affect all in the same manner—some become thoughtful others hilarious and some destructive. They feel they can accomplish almost impossible feats with ease and the moral sense is completely submerged. Memory of actions done under its influence are obliterated.

The chronic effects lead to a progressive depreciation of mentality, tremors, physical weakness, anorexia, pallor, icterus and decrease of sensation and sexual power. There is reduction of will power and concentration. In the most extreme cases maniacal or melancholic symptoms appear and in some there is a condition allied to delirium tremens with hallucinations and destructiveness. Coma lasting some hours is common in those who desire its full effect.

*Cannabis indica* has been used for many years in therapeutics as a sedative and an analgesic but recently it has been supplanted by other drugs.

The outlook for the addicts is serious. It is not as yet certain that withdrawal symptoms are important but rather that depreciation of the higher centers is more or less permanent and the desire to be cured is wanting.

The treatment is similar to that of other drug addictions such as heroin and cocaine except that withdrawal symptoms are not prominent. On the other hand the moral comeback may require prolonged care and close control. Fatalities from its use are rare although there may be pronounced respiratory and circulatory depression associated with unconsciousness. Recovery from this may take twelve to thirty-six hours.

## BARBITURATES

With the recent introduction of preparations containing barbituric acid and its allied compounds, there has been an increasing incidence of poisoning from these substances. They have become a household remedy for all and sundry causes of restlessness, insomnia, and other results of mental agitation. There is no doubt that many cases of poisoning by these compounds are mild attempts at suicide or at least are prompted by the desire to forget mental perturbation.

The principal preparations of this group that have recently been reported as causes of death are the following.

Veronal	Somnifen
Medinal	Nembutal
Allonal	Amytal
Pernocton	Ceronal
Phenobarbital (luminal)	Phruadorm
Severnal	Gardenal
Dial	Evipan

These are undoubtedly a greater menace to life than is usually appreciated by the laity.

**Symptoms**—The symptoms are a deep narcosis with stertorous respirations at first which later become rapid and shallow when many fine rales are heard in the chest indicating a degree of pulmonary exudate or edema. There are pyrexia, tachycardia, cyanosis and a leucocytosis which would all indicate pulmonary congestion even to a bronchopneumonia. The depth of the narcosis and the severity of the pulmonary manifestations are in direct proportion to the amount of the drug taken. The sleep may last for many days and respiratory depression may become alarming. The reflexes are all depressed or absent and there is often incontinence of urine and feces.

In addition to the above there is a group of people with a peculiar susceptibility to some of these preparations which are compounded with amidopyrine such as allonal, aseiatin, cibalin, comfral, oftalidon, somnasal, veramon, and veropyron. In these patients a profound leucopenia develops which leads to symptoms and signs identical with those described under granulocytopenia or agranulocytic angina.

Skin rashes of an erythematous type are common even with small amounts. There are other symptoms of milder toxicity than those described above. These are headache, vertigo, ataxia, ocular disturbances and indistinct vision. In susceptible individuals all these symptoms and even delirium, coma and vasomotor collapse may follow comparatively small amounts.

**Diagnosis**—The diagnosis is suggested by the narcosis and the presence of evidence that the patient has had such drugs in his possession or has been in the habit of taking them for insomnia.

**Prognosis**—The prognosis depends upon the amount of the drug taken. There are cases on record which have recovered after being unconscious for eight days. Respiratory failure and pulmonary infections are the usual causes of death.

**Treatment**—The treatment consists in maintaining respiration and the prevention of aspiration of foreign materials and secretions. Inhalation of a mixture of carbon dioxide and oxygen is indicated when there are tachypnea and cyanosis. If the respirations become irregular or there are periods of apnea artificial respiration must be instituted, or better still the patient placed in a Drinker respirator if one is available. The usually accepted stimulants such as strychnine, digitalis, and camphor are of doubtful value. Coramine and lobeline have been more recently advocated. Analeptics such as benzedrine and picrotoxin should be given in full doses short of convulsions. They must be continued regularly until the patient shows returning consciousness or until a fatal issue has occurred. The patient should be placed in a semireclining position and if there is any danger of aspiration through depression of the swallowing reflex food should be given by nasal feeding or a stomach tube. Fluids are given by rectum with the Murphy drip method. Careful nursing is of the greatest importance.

## LEAD

Lead has been used in industry and arts for centuries and for most of these it has been well known that there was some association between its use and the appearance of divergent groups of symptoms. But it remained for Tanquerel des Planches in 1831 to correlate them.

**Incidence**—Whereas up to about 1920 lead poisoning was by far the greatest industrial intoxication it has conspicuously decreased since by the institution of preventive measures. These are now controlled by legislation and improved working conditions and education have done a great deal also to reduce its incidence.

**Etiology**—Lead may enter the body by ingestion, inhalation through the mucous membranes or the skin through hair dyes, cosmetics and abrasions upon which lead lotions have been applied. Lead enters the gastrointestinal tract through contaminated foods or liquids. Acidulated water in contact with lead pipes or worms may dissolve sufficient lead as carbonate to produce intoxication. Food contaminated by lead from unclean hands, chewing tobacco and snuff with lead wrappers, painted cots, toys and other articles which children may gnaw or chew may all cause intoxication. Devonshire colic from contaminated cider and colica pectorum from lead being added to wine to prevent its souring were well known causes of epidemics many years ago. Lead salts taken for suicidal purposes or to promote abortion are other ways by which it is ingested. But the most dangerous portal of entry is through the respiratory tract. Whereas the greater part of the ingested lead can be handled by the liver that inspired is rapidly distributed through the body and can thus exert a concentrated toxic effect. It is principally inspired as dust in the form of white or red lead or as fumes from burning wood impregnated with lead in poorly drawn stoves in unventilated rooms.

Hair dyes and cosmetics are relatively common but often neglected means by which lead gains entrance to the body. Other portals which are often over

looked are lead acetate douches, lead fomentations and lotions, and astringent mouthwashes. The latter are not necessarily swallowed to produce intoxication.

**Symptoms**—The symptoms of lead poisoning may be fulminating or chronic, and in the latter group the association of cause and effect may be difficult to detect.

**Acute lead poisoning** differs in no essential way from the chronic, except for the violence and suddenness of the symptoms. These are principally nervous and hematological manifestations. There may be acute weakness and convulsions followed by coma commonly called 'lead encephalopathy'. In other cases an acute anemia occurs which may be so intensively destructive as to produce hemoglobinuria. In less acute cases gastrointestinal symptoms may be more prominent. They consist of nausea, vomiting, abdominal colic and constipation, simulating intestinal obstruction with which it may be confused and the patient may be operated upon. Diarrhea or rather tenesmus, may sometimes be present. The period of exposure is less important in the acute cases than is the amount absorbed or inhaled although in some who are relatively susceptible this may be comparatively small.

**Chronic lead poisoning** may present a variety of different symptom patterns which often overlap in varying degrees in different cases. For convenience of description they may be described under the following headings.

**Gastrointestinal System—Lead Colic**—One of the earliest symptoms of lead poisoning, of which the patient complains is abdominal colic with associated constipation. The colic is usually felt about the umbilicus and the lower abdomen being therefore particularly referred to the areas of visceral pain resulting from small intestinal and colonic spasm. The writer was able many years ago to view these spasms during the course of an operation for presumed intestinal obstruction. The intermittent segmental contraction of the small bowel and the colon presented a very striking picture. The abdominal wall is usually retracted but not rigid which with the absence of leucocytosis but a relative lymphocytosis and no pyrexia helps to differentiate lead colic from acute peritoneal inflammation. The author however has seen cases of acute lead poisoning with a leucocytosis as high as 22 000 per cumm.

In cases of suspected lead poisoning, the so called 'blue line' on the gums should be looked for. It appears as a serrated or dotted line on the gum margin and can be well seen by the aid of a hand glass. It is to be differentiated from staining of the teeth. It is due to deposits of lead sulphide about the minute blood vessels in the papillae of the gums and is most evident when pyorrhea is also present. It is almost pathognomonic of the presence of lead and may be noted when the amount absorbed has not been sufficient to produce toxic symptoms. It is simulated by a similar line caused by bismuth.

**Hematological System**—There often appears before the onset of lead colic a progressive pallor which is contributed to by destruction of the erythrocytes. The pallor is not altogether due to the anemia. This anemia is associated with a compensatory stimulation of the bone marrow. In addition the red cells show a basophilic granulation or stippling. These cells are presumed to be degenerating young reticulocytes. Although they are present





Fig 310 — A case of lead poisoning showing the blue line on the margin of the gums



in other conditions, such as pernicious anemia and leucemia, they are most abundant in lead poisoning, and when numerous are an important point in the diagnosis.

**Nervous System**—It has already been mentioned how in acute lead poisoning convulsions and coma may develop and are known as 'lead encephalopathy'. This may also occur in the more chronic cases. In addition many victims of lead poisoning may develop mental depression, occasionally delirium, and more rarely, acute mania with delusions. In one group convulsions may be prominent, while in another the condition progresses to simulate general paresis.

**Lead palsy** has been recognized for many years, and was graphically described by Benjamin Franklin early in the eighteenth century. The first evidences of it are weakness and tremor. The latter is quite characteristic and is best elicited by the outstretching of the hands. The weakness becomes progressive until paralysis may develop. As a rule it is painless. The groups of muscles most used are those most affected, as in locomotor ataxia. Therefore the right hand and arm are usually worse than the left; developing finger and wrist drop as the extensors are more affected than the flexors. In the leg peroneal paralysis is the most common. There may also be optic neuritis. It has recently been suggested that certain cases usually classified as disseminated sclerosis may be due to lead poisoning.

**Miscellaneous**—For many generations gout has been associated with lead poisoning. Reference has already been made to this (page 670). It has also been suggested, and clinical evidence presented, that during attacks of acute lead poisoning there is a temporary hypertension. The association of primary contracted kidney and lead intoxication has been recognized for many years. Whether the ensuing degenerative renal changes are primarily caused by lead or are secondary to the interlobular lesion is not as yet clear. It is however, one of the three principal conditions associated with this renal change (lead gout, essential hypertension).

Lead poisoning in children has recently been recognized as an important cause of disability. It has been stated above how they may ingest lead through gnawing painted toys and furniture of the cheaper kinds. The symptoms closely simulate those in adults, but there are certain ones which are more distinctive than others. As children are subject to convulsions and gastrointestinal disturbances from many causes, they are not particularly indicative of lead poisoning. On the other hand the outstanding sign is stippling of the erythrocytes. The x-ray pictures of the growing bones reveal white lines representing increased density. These may be in series, progressing toward the metaphysis.

**Diagnosis**—The diagnosis of lead poisoning rests principally upon the appreciation of the possibility that intoxication has occurred. This is important when either the gastrointestinal neurological or hematological symptoms dominate the clinical picture. The diagnosis of lead poisoning rests upon finding the 'blue line' in the gums and the presence of numerous basophilic granulations or stippled cells in blood smear. Absolute con-

firmation is obtained by detecting lead in the feces or urine. It is much more abundant in the former. During the periods when the greater part of the lead is found in the bones, little excretion may take place. In all cases of unexplained anemia or neurological lesions, lead poisoning should be suspected.

**Prognosis**—The course of lead poisoning is usually chronic, although at any time acute exacerbations with toxic symptoms may occur which give to the disease a certain irregular periodicity. These periods are coincident with a low calcium diet or a mild acidosis. Lead is also released from the bones during periods of intercurrent infection which makes the diagnosis difficult as lead intoxication is masked by the presence of the more obvious condition.

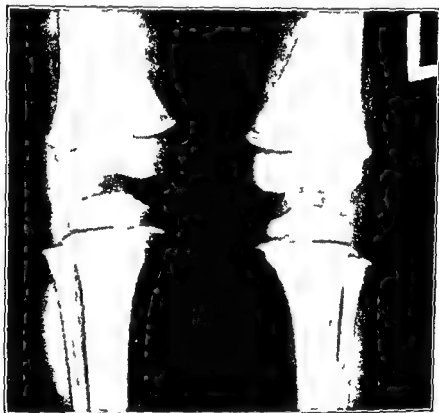


Fig. 14—X-ray of the knee joint of a patient suffering from lead poisoning. Note the lines of increased density at the end of the bone.

Death may occur either from acute lead encephalopathy, diffuse peripheral neuritis (sometimes simulating Landry's paralysis), chronic debility with intercurrent infection or uremia in those chronic cases where cardiovascular renal lesions are prominent.

**Treatment**—The prophylaxis of lead poisoning is of the first importance in occupations where lead is used. Every precaution should be taken against its ingestion or inhalation. Lead should be prohibited in all apparatus used in distilling or condensing liquids for human consumption. Employees working in lead dust should be protected with respirators and lead must not be allowed to form part of cosmetics. Lead paint should not be permitted on toys, cots and

other indoor or outdoor furniture which may be accessible to infants. The more unusual means whereby lead may enter the body are preventable chiefly through education.

The active treatment of lead intoxication falls under two headings

- 1 Treatment of the immediate toxic symptoms
- 2 Removal of lead from the body or 'deleading'

The toxic symptoms from lead are due to its circulation throughout the body. If this can be prevented by elimination or by fixation in the bones, the symptoms will at least temporarily be relieved. In the acute stages it is best to fix the lead in the bone. It has been well demonstrated that any measure which increases the retention of calcium in the bones also binds lead. Therefore a high calcium diet will operate to this end and the best means of accomplishing this is by giving a diet rich in calcium, containing such foods as egg yolk, cheese, milk, almonds, beans, oatmeal, turnips, carrots and oranges, and calcium lactate or gluconate in amounts of 2 to 4 grams daily. This may be aided also by an alkaline diet or alkalis. If there are acute cerebral symptoms or serious anemia, calcium gluconate should be given intravenously, 10 cc of a 10 per cent solution. Calcium chloride must be avoided as it may produce an acidosis which releases lead from the stores in the bones.

Urgent symptoms are usually rapidly controlled by these measures but if not sedatives may be required for the nervous symptoms, and morphine is particularly helpful for the intestinal colic.

After having relieved the acute toxic symptoms the time has then arrived to proceed with removing the lead or 'deleading' the patient. This however must be undertaken with caution to avoid suddenly flooding the blood stream with lead and so reproduce the acute symptoms. The process is the opposite to its fixation. A low calcium diet consisting of bread, potatoes, rice, tomatoes, bananas, apples, corn meal, tea, coffee and some other vegetables and fruits will gradually release calcium and consequently lead from the bones. This may be hastened by producing a mild acidosis preferably with ammonium chloride rather than the calcium salt. But this must be used cautiously as it may likewise release the lead too rapidly. Potassium iodide also increases the elimination of lead and similar caution must be observed. Lead is secreted principally through the bowel and in less amounts in the urine.

## MERCURY

Mercury poisoning may be produced in a number of ways. The more important are the ingestion of mercury bichloride with suicidal intent or accidentally during the mercurial treatment of syphilis and in industries particularly in quicksilver mines and in the beaver or velvet hat trade. When strong mercurial solutions were used for douches absorption by the vaginal and uterine mucosa was a common cause of intoxication.

Mercury poisoning may vary in degree from an acute fulminating type to an extreme chronicity. The severity of the symptoms depends entirely upon the amount of mercury absorbed in a unit of time and the susceptibility of the individual. As much as  $1\frac{1}{2}$  grams (0.1 gram) has caused

firmation is obtained by detecting lead in the feces or urine. It is much more abundant in the former. During the periods when the greater part of the lead is found in the bones, little excretion may take place. In all cases of unexplained anemia or neurological lesions, lead poisoning should be suspected.

**Prognosis**—The course of lead poisoning is usually chronic, although at any time acute exacerbations with toxic symptoms may occur which give to the disease a certain irregular periodicity. These periods are coincident with a low calcium diet or a mild acidosis. Lead is also released from the bones during periods of intercurrent infection which makes the diagnosis difficult, as lead intoxication is masked by the presence of the more obvious condition.

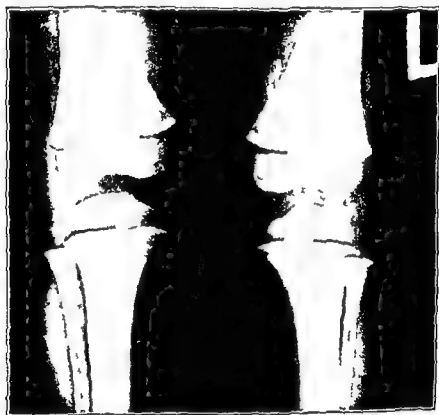


Fig. 14.—X-ray of the skull of a child suffering from lead poisoning. Note the lines of increased density at the ends of the bones.

Death may occur either from acute lead encephalopathy, diffuse peripheral neuritis (sometimes simulating Landry's paralysis), chronic debility with intercurrent infection or uremia in those chronic cases where cardiovascular renal lesions are prominent.

**Treatment**—The prophylaxis of lead poisoning is of the first importance. In occupations where lead is used every precaution should be taken against its ingestion or inhalation. Lead should be prohibited in all apparatus used in distilling or condensing liquids for human consumption. Employees working in lead dust should be protected with respirators and lead must not be allowed to form part of cosmetics. Lead paint should not be permitted on toys, coats and

other indoor or outdoor furniture which may be accessible to infants. The more unusual means whereby lead may enter the body are preventable chiefly through education.

The active treatment of lead intoxication falls under two headings

- 1 Treatment of the immediate toxic symptoms
- 2 Removal of lead from the body or 'deleading'

The toxic symptoms from lead are due to its circulation throughout the body. If this can be prevented by elimination or by fixation in the bones the symptoms will at least temporarily be relieved. In the acute stages it is best to fix the lead in the bone. It has been well demonstrated that any measure which increases the retention of calcium in the bones also binds lead. Therefore a high calcium diet will operate to this end and the best means of accomplishing this is by giving a diet rich in calcium containing such foods as egg yolk, cheese milk, almonds, beans, oatmeal, turnips, carrots and oranges and calcium lactate or gluconate in amounts of 2 to 4 grams daily. This may be aided also by an alkaline diet or alkalis. If there are acute cerebral symptoms, or serious anemia, calcium gluconate should be given intravenously 10 cc of a 10 per cent solution. Calcium chloride must be avoided as it may produce an acidosis which releases lead from the stores in the bones.

Urgent symptoms are usually rapidly controlled by these measures, but if not, sedatives may be required for the nervous symptoms, and morphia is particularly helpful for the intestinal colic.

After having relieved the acute toxic symptoms the time has then arrived to proceed with removing the lead or 'deleading' the patient. This however must be undertaken with caution to avoid suddenly flooding the blood stream with lead and so reproduce the acute symptoms. The process is the opposite to its fixation. A low calcium diet consisting of bread, potatoes, rice, tomatoes, bananas, apples, corn meal, tea, coffee and some other vegetables and fruits will gradually release calcium and consequently lead from the bones. This may be hastened by producing a mild acidosis preferably with ammonium chloride rather than the calcium salt. But this must be used cautiously, as it may likewise release the lead too rapidly. Potassium iodide also increases the elimination of lead and similar caution must be observed. Lead is secreted principally through the bowel and in less amounts in the urine.

## MERCURY

Mercury poisoning may be produced in a number of ways. The more important are the ingestion of mercury bichloride with suicidal intent or accidentally, during the mercurial treatment of syphilis and in industries particularly in quicksilver mines and in the beaver or velour hat trade. When strong mercurial solutions were used for douches absorption by the vaginal and uterine mucosa was a common cause of intoxication.

Mercury poisoning may vary in degree from an acute fulminating type to an extreme chronicity. The severity of the symptoms depends entirely upon the amount of mercury absorbed in a unit of time and the susceptibility of the individual. As much as  $1\frac{1}{2}$  grains (0.1 gram) has caused

death, while others have recovered from as much as 30 grains (2 gm). If the mercury is ingested, the severity of toxic effects will depend upon the time which elapses between its ingestion and the induction of vomiting and the amount originally taken. On the average, 19 grains (1.25 gm) with vomiting delayed for over half an hour results in death. The liver does not handle mercury to the same extent as it does lead and arsenic because it may appear in the urine within a few minutes after its ingestion, although the principal avenue for its excretion is through the colon.

### Acute Mercury Poisoning

Acute mercury poisoning is usually produced by the ingestion of mercury bichloride and has been a favorite method of suicide.

**Symptoms**—The symptoms may be divided into two stages. Immediately after the poison has been ingested there is a metallic taste in the mouth. Within a few minutes epigastric discomfort is felt, which shortly amounts to acute pain. Nausea soon supervenes and if there be immediate vomiting and the stomach is thoroughly emptied the chances of recovery are improved. In some, vomiting is delayed although there is intense nausea and retching.

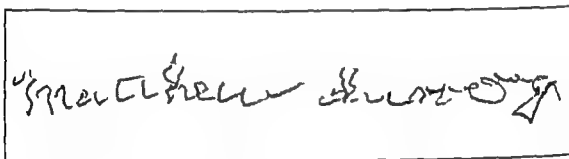


Fig. 1.—Handwriting of man with bloody ink as (secret) of Dr. Daniel T. Hunter.

Retching is constant with eventually intense vomiting, and the vomitus may contain blood stained mucus and desquamated mucosa. The severe abdominal cramps become general and are soon accompanied by diarrhea, tenesmus and bloody stools. There may also be collapse and death within twenty-four to forty-eight hours. In these cases the principal anatomical findings are an intense hemorrhagic gastroenteritis and colitis with early hepatitis. There is also a leucocytosis. All of these gastrointestinal symptoms may vary considerably according to the amount of poison taken and naturally the intestinal and colonic features will depend upon the amount which passes through the stomach.

The second important group of symptoms are those arising from the action of the mercury upon the kidney. There is an early oliguria. Such urine as is passed contains blood, albumin and many casts. There may be complete anuria. The interference with renal function is reflected in a steady increase of the nonprotein nitrogen, urea, creatinine and uric acid of the blood. There is also a progressive acidosis with declining carbon dioxide combining power. A moderate hypertension and slight general edema may fol-



low. These cases either pass into a state of uremia, or if the damage is of a milder degree, renal function may be re established in a few days, and complete recovery follow. If the anuria persists longer than four days, a fatal result is to be expected.

Anatomical changes in the kidneys are necrosis of the epithelium of the convoluted tubules, and to a lesser degree, of Henle's loops. At the same time evidence of regeneration may be detected. The patient may continue to appear in relatively good condition for many days and his appearance does not indicate the severity of the renal lesion.

The causes of death in acute mercury poisoning are either collapse uremia, or infection from the acute gastroenterocolitis and stomatitis.

**Diagnosis**—The diagnosis in these acute cases depends principally upon the history of the ingestion of mercury usually in the form of bichloride, or its detection in the vomitus or stools by the electrolytic method.

**Prognosis**—The prognosis has already been indicated as depending upon the amount ingested and the time elapsing before the stomach is emptied either by vomiting or gastric lavage or both.

**Treatment**—The treatment in the acute stages is principally the removal of mercury from the stomach. If collapse occurs this is treated by the usual methods while the treatment of renal failure is the same as that indicated in acute nephritis. This has now been improved by the use of the artificial kidney where by peritoneal dialysis or by washing the venous blood through a dialyzable membrane the mercury and the noxious retention products may be eliminated and the nonprotein nitrogen may be brought to normal. It requires expert attention. This principle rests upon the fact that acute mercury poisoning causes a self limited lesion in the kidney which is reversible if life can be sufficiently prolonged.

### Chronic Mercury Poisoning

A subacute or chronic form of mercury poisoning may be found in those who are being treated for syphilis with mercury and in industries where mercury is employed. In the latter it is usually acquired through the respiratory tract as the mercury is in a vaporous form as in quicksilver mines the manufacture of thermometers and barometers and all explosive fulminants of mercury.

**Symptoms and Signs**—The symptoms and signs of the subacute form are those of an intense ptyalism. There is first the characteristic metallic taste in the mouth soon followed by salivation and stomatitis. The teeth are loosened and tender on pressure and the gums are swollen and have a bluish grey color as has also the mucous membrane of the tongue and mouth. There is a distinctive fetor to the breath. As the stomatitis progresses areas of necrosis appear on the tongue and mucous membrane of the cheeks and the cervical glands become enlarged. The necrotic processes may extend to the bone principally the mandible.

There is also a more chronic form in which the stomatitis is not so prominent. This occurs principally in those employed in quicksilver mines and in the hatters trade and more recently it has been reported in France in women

managing shooting galleries, the poisoning being derived from the fulminant mercury fumes from the exploding caps of the cartridges. A good description is found in the "Mad Hatter" in *Alice in Wonderland*, and in New England it is known as "Danbury Shakes." The outstanding feature is a fine but intermittent tremor in the hands. It is of the intentional variety and is aggravated by excitement and confusion, and these people often acquire a timid and sensitive nature. The tremor is well demonstrated in the character of their handwriting.

In 1942 Atkinson described a brownish colored reflex from the anterior capsule of the lens in those who worked for a long time with mercury or in an atmosphere containing mercury although there were no symptoms of mercurialism (see Figs. 516 and 517). This is believed to be due to a deposit of mercury on or in the anterior capsule and appears to be permanent.

The diagnosis is not difficult and the prognosis depends upon the duration of the illness. The treatment is confined entirely to removal from the environment of this chemical.

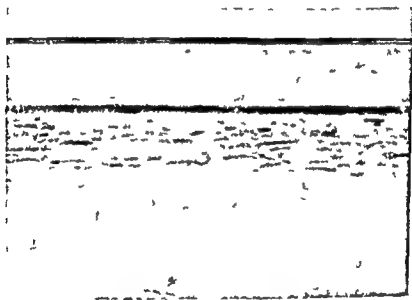


Fig. 18. Micrograph of the reflection of light from the anterior capsule of the lens showing the deposit of mercury. (Courtesy of Walter S. Atkinson, from *Acta Ophthalmologica* Society, 1946.)

## ARSENIC

Arsenic at one time was an important cause of epidemic intoxications, as for instance from the use of contaminated glucose or sulfuric acid in the manufacture of beer by the use of malt prepared with coke impregnated with arsenic, molds setting free fixed arsenic from wall papers, cosmetics containing arsenic, and in submarines through the arsenical fumes arising from the contents of the electric accumulators.

Acute arsenic poisoning due to suicidal or homicidal attempts falls into the realm of toxicology except so far as it arises from the therapeutic use of arsenic in the treatment of syphilis. This has already been dealt with (Chapter XIX).



Fig 316.—Drawing of the slit lamp beam showing a red reflex from the lens (Courtesy of Walter S. Atkinson Trans American Ophthalmological Society 1940)

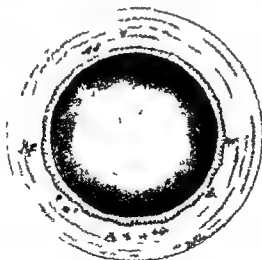


Fig 317.—Drawing to show the gray reflex of the lens on oblique illumination (Courtesy of Walter S. Atkinson Trans American Ophthalmological Society 1940)



**Chronic arsenical poisoning** may be found in those who are exposed to it in their occupation, and comes from the absorption of small amounts over a prolonged period. The onset is insidious, and the symptoms so indifferent as to be quite confusing. There are usually at first weakness with dyspepsia, anorexia, nausea and vomiting of mucus. If the atmosphere contains a toxic amount of arsenic, there may be nasopharyngeal catarrh, hoarseness, conjunctivitis, and in the more chronic cases indolent necrosis of the nasal cartilage. Skin eruptions are most important. There are usually erythema and swelling about the scrotum, perineum, axillae and groins where the skin is moist. Ulceration may occur. There is finally a generalized greenish pigmentation with gradually a patchy and coalescent hyperkeratosis, chiefly on the palms and soles.

In addition to this sign there is often a low grade pyrexia and jaundice. The nervous system is particularly susceptible to its action, this leads to a form of peripheral neuritis chiefly indicated by sensory signs such as tingling, formication, burning pain and anesthesia. Motor paralysis is rare. The cranial nerves are seldom affected although optic neuritis has been reported and mental deterioration occurs in the most chronic states.

**Diagnosis**—The diagnosis usually rests upon the proof of exposure, but is suggested by the dermatological and neurological signs, and jaundice. The detection of arsenic in the stools or urine in abnormal amounts is conclusive.

**Prognosis**—The prognosis depends upon the acuteness and severity of the intoxication. Those chronically exposed may develop a remarkable tolerance as among the "arsenic eaters" of Styria, some of whom take 800 to 1000 mg. a week. There are persons who are quite sensitive; this is one of the dangers in the arsenical treatment of syphilis.

**Treatment**—The treatment consists of stopping the intake and hastening elimination by free diuresis and catharsis. Calcium thiosulphate intravenously in amounts of 10 cc. of a 5 per cent solution every other day, appears to help relieve the immediate symptoms. The specific antidote substance used against Lewisite is also of great value in acute and chronic arsenical poisoning. It seems to be specially useful in exfoliative dermatitis.

## PETROLEUM OR GASOLINE

The increasing use of internal combustion engines operated with gasoline or petroleum, and the constant use of these substances as household articles have produced a large number of poisonings from them. The fumes of gasoline present in the exhaust of these engines particularly if they are running in a confined and poorly ventilated space such as in tunnels or closed garages may produce an acute intoxication. It is difficult to be certain how much of this disability is due to the gasoline fumes, and how much to carbon monoxide. Experimentally pure gasoline fumes produce erythema, salivation, restlessness, muscular relaxation, coma and sometimes convulsions.

**Symptoms**—In man the specific symptoms are more commonly found when these chemicals are ingested either intentionally or by mistake. It is not unusual for children to swallow them. They do not produce any symptom in

the gastrointestinal tract, but when it volatilizes in the mouth and pharynx during the act of swallowing, the fumes are inhaled. If in high concentration there is rapid unconsciousness, twitching, convulsive seizures, and dilatation of the pupils. These represent its anesthetic effect. If the fumes have been still further concentrated signs of asphyxia develop. There is cyanosis, slowing respiration, and eventually respiratory failure. When they are absorbed from the gastrointestinal tract the fumes are eliminated through the lungs and through local irritation produce congestion, edema and bronchopneumonia. In these cases there is tachypnea, pyrexia, and a taste of gasoline in the mouth for many days and even weeks.

The treatment is purely symptomatic.

### ERGOT

Ergot poisoning is principally of a chronic type although acute cases are rarely encountered. Chronic ergot poisoning is mainly caused by eating bread made from rye (black bread) the grain of which has been contaminated by a parasitic fungus (*Claviceps purpurea*).

**Symptoms**—The symptoms are of two types of poisoning, the convulsive and the gangrenous.

The convulsive ergotism is characterized by headache, muscular cramps, epileptiform convulsions, and a small hypertensive pulse. These may be preceded by vertigo and an itching, crawling sensation in the skin. In the severest cases somnolence, stupor and coma may develop while in others there may be acute mania. Associated with the muscular cramps there are tremors and contractures.

Gangrenous ergotism presents a picture somewhat similar to that described under certain diffuse vascular diseases such as thromboangitis obliterans, Raynaud's disease and erythromelalgia, and also may approximate in its early forms to the lesions of scleroderma and dermatomyositis. There is apparently a progressive pressor effect upon the arterioles of the extremities and necrosis of pullover on the toes, fingers, nose, ears and external genitalia are followed by gangrene of these parts. An entire limb may be so affected. Vesiculation with infection may lead to moist gangrene but in most cases it is of the dry type.

**Treatment**—The treatment of course is principally prophylactic. When the signs and symptoms first develop every precaution should be taken to prevent further ingestion of this substance. The local vascular lesions are treated in the same manner as thromboangitis obliterans and Raynaud's disease.

### FOOD

Many groups of symptoms are laid at the door of food poisoning and the diagnosis is used too loosely both by the laity and the profession. There has been mentioned in the chapter on Diseases of Allergy that many individuals have a susceptibility to certain foods. Although these could be termed "food poisoning" as far as the individual is concerned it cannot be so applied in the proper sense of the term, as it is the individual and not the food that is

at fault. Many infections such as typhoid fever, bacillary dysentery, cholera undulant fever, and tuberculosis are acquired through the ingestion of food, water, and other materials contaminated by the specific organisms, and might with reason be considered as "food poisonings." It is best, however, to confine this term to two distinct entities: one of which is due to specific groups of organisms, and the other is caused by a specific toxin which is produced by an organism outside the body.

### FOOD INFECTION

The *salmonella* group of bacteria occupies an intermediate place bacteriologically between the coli and typhoid bacilli, and is sometimes called the intermediate group or the hog cholera, the enteritides, or the paratyphoid group. Among these are found the specific organisms which produce food infection: the principal ones being *Salmonella enteritidis* (Gaertner bacillus), *Salmonella cholerae suis* (Hog cholera bacillus) and the *Salmonella aertrycke*. All of them are gram negative nonspore bearing aerobic bacilli which do not ferment lactose.

Another group of bacteria is the *Staphylococcus* of which the *aureus* is the most potent. This is often the cause of severe local epidemics through the ingestion of infected foodstuffs chiefly custards, pies, ice cream, etc.

**Symptoms**—The incubation period is from four to twelve hours. The onset as a rule is acute. The first symptoms are nausea, epigastric pain soon followed by vomiting and diarrhea. The pain is of the colicky character and is sometimes most intense. The stools are watery, have a foul odor, and their greenish color indicates the irritation of the small bowel. There is pyrexia, malaise, weakness and prostration. As a result of the vomiting and diarrhea, thirst and dehydration rapidly develop with oliguria.

The severity of these symptoms varies considerably not only in individuals but also in different epidemics. In some they are fulminating and fatal within forty-eight hours. Their intensity is apparently due to the mass of infection and the virulence of the organisms.

**Diagnosis**—The specific diagnosis of a *salmonella* or *staphylococcus* infection is often difficult. There may be a history of having eaten tainted food; often it is difficult to be certain of this. It usually suggested itself to the mind of the patient by the development of the symptoms. The cause may be suspected but a specific diagnosis can be arrived at only by the isolation of the organism from the suspected food or from the blood, urine and feces of the patient. This is seldom done except in well defined epidemics. Agglutinins appear in the blood serum about a week after the onset of the disease and at this time the organisms have usually disappeared not only from the blood but also from the stools and the urine.

**Prognosis**—The prognosis varies considerably from epidemic to epidemic. The majority of cases recover with a prolonged convalescence. The mortality is variously estimated as between 1 and 2 per cent.

**Treatment**—The treatment is purely symptomatic. Vomiting should not be prevented and gastric lavage should be supplemented to assist in removing from the stomach any remains of the infected material. High colonic irriga-

tions may give some relief to the intense diarrhea. The acute abdominal pain and cramps may be alleviated by hot applications, and in many instances morphia may be required. The dehydration resulting from the vomiting and diarrhea should be corrected by high fluid intake, and if necessary, intravenous saline glucose injections.

## FOOD INTOXICATION

### (Botulism and Allantiasis)

In distinction to food infection food intoxication is the result of the ingestion of a virulent toxin produced by the *Clostridium botulinum* which is a spore bearing, anaerobic bacillus. It is a true intoxication the toxin being preformed before ingestion. It occurs both in man and certain of the lower animals particularly chickens, turkeys, ducks and water fowl (especially the wild duck). It is conveyed to man by contaminated preserved foods in which the bacillus has produced a varying amount of toxin. At one time it was considered to arise only from potted meats but it has been clearly demonstrated that it may be present in preserved fruits and vegetables or in any food that contains protein. The careful inspection of the manufacture of processed foods has led to a great reduction in the incidence of epidemics. The majority of outbreaks are due now to foods preserved at home where they are not properly sterilized under pressure to destroy the spores of these bacteria.

**Symptoms**—The incubation period is from twelve to twenty-four hours but shorter periods have been reported probably due to the ingestion of a large quantity of toxin. The onset is insidious but rapid. The principal symptoms of botulism or food intoxication are weakness and paralysis. The cranial nerves are conspicuously involved. Gastrointestinal symptoms are not due to botulism but to some other concurrent infection. There is a progressive involvement of the peripheral nerves. Disturbances of vision appear early followed by blepharoptosis, diplopia, difficulty in talking, swallowing and regurgitation of food through the nose due to paralysis of the palate when aspiration into the trachea may occur. On examination the pupils are dilated, there is absence of the light reflex and nystagmus. The general muscular weakness is intense but there are no sensory disturbances and the disease is painless.

The systemic symptoms are subnormal temperature, at first a bradycardia and then a tachycardia, dyspnea and cyanosis due to respiratory paralysis which is the most common cause of death.

**Diagnosis**—The diagnosis of this disease rests upon the characteristic symptomatology and the occurrence of the disease in a number of persons who have consumed the same food. The absolute diagnosis rests solely upon the demonstration of the toxin by injection of tainted food into susceptible animals or the isolation of the organisms by suitable bacteriological methods. There should be little difficulty in differentiating it from food infection. On the other hand confusion may arise in distinguishing this condition from certain cases of encephalitis. In botulism there is no change in the cerebrospinal fluid, an important point in distinguishing it from cerebrospinal virus infections.



**Treatment**—There is a specific botulism antitoxin, the efficacy of which depends principally upon its early administration. Experimentally it is curative, but not after respiratory symptoms have developed. In man its administration is frequently too long delayed. It has been found experimentally that morphine delays the effect of the toxin. As death is usually due to respiratory failure, and as the toxin is eventually destroyed or eliminated, it is important that artificial respiration be maintained either by the Schaefer method or better in a respirator, as long as life can be prolonged. Some borderline cases are undoubtedly saved by this means.

### SNAKE BITES

From a practical point of view all snake bites should be considered as possibly poisonous. Practically all snakes have a gland corresponding to the parotid of mammals which secretes a toxic substance. These venom glands are connected with the hollow or grooved fangs of the snake and when a person is "bitten" by them (or stabbed by vipers) the venom is injected subcutaneously. A goodly number of treatises have been published on snake bites and those who are particularly interested are referred to some of these.

The venom toxins are in general twofold, the hematoxin and the neurotoxin. The former produces hemolysis, hemorrhagic extravasations, edema and local destruction of tissue while the latter specifically attacks the nerve centers and produces paralysis of the medullary functions. Both these toxins are usually present in all venoms but in different proportions.

Fresh venom when collected is colored a deep amber to a yellowish green and appears as a viscid fluid. It is usually soluble after drying. The venom of the viper is a good example of one that contains large amounts of the hematoxin. The snakes of this type most frequently found in America are the rattlesnake, copperhead and the moccasin. The cobras on the other hand, represent those whose venom is principally neurotoxic and in America the coral snake is the best representative of this species.

**Symptoms**—The symptoms naturally vary with the predominating toxin injected. Those produced by a hematoxic venom are usually a burning pain at the site of inoculation, a rapidly extending edema and dark discoloration of the skin due to extravasation of blood and destruction of the tissues. There are nausea and vomiting, vertigo rapidly followed by prostration, cold, clammy sweat and coma. The temperature is subnormal, there is low blood pressure and death may occur in a comparatively short period. During recovery jaundice is not unusual. If a patient recovers from the acute hematoxic effects, generalized edema may remain which when infected leads to extensive suppuration and gangrene.

The inoculation of a venom containing principally neurotoxin produces much less local reaction and the signs of collapse are less severe. The principal feature is dyspnea due to respiratory paralysis.

There is little doubt about the *diagnosis*.

**Prognosis**—The prognosis depends upon the type of snake bite and the duration before specific treatment is instituted, the mortality varying with the different species from 10 to 35 per cent.

tions may give some relief to the intense diarrhoea. The acute abdominal pain and cramps may be alleviated by hot applications and in many instances morphia may be required. The dehydration resulting from the vomiting and diarrhoea should be corrected by high fluid intake, and if necessary, intravenous saline glucose injections.

## FOOD INTOXICATION

### (Botulism and Allantianis)

In distinction to food infection food intoxication is the result of the ingestion of a virulent toxin produced by the *Clostridium botulinum* which is a spore bearing, anaerobic bacillus. It is a true intoxication the toxin being preformed before ingestion. It occurs both in man and certain of the lower animals particularly chickens, turkeys, ducks and water fowl (especially the wild duck). It is conveyed to man by contaminated preserved foods in which the bacillus has produced a varying amount of toxin. At one time it was considered to arise only from potted meats but it has been clearly demonstrated that it may be present in preserved fruits and vegetables or in any food that contains protein. The careful inspection of the manufacture of processed foods has led to a great reduction in the incidence of epidemic. The majority of outbreaks are due now to foods preserved at home where they are not properly sterilized under pressure to destroy the spores of the bacteria.

**Symptoms**—The incubation period is from twelve to twenty four hours, but shorter periods have been reported probably due to the ingestion of a large quantity of toxin. The onset is insidious but rapid. The principal symptoms of botulism or food intoxication are weakness and paralysis. The cranial nerves are conspicuously involved. Gastrointestinal symptoms are not due to botulism but to some other concurrent infection. There is a progressive involvement of the peripheral nerves. Disturbances of vision appear early followed by blepharoptosis, diplopia, difficulty in talking, swallowing, and respiration of food through the nose due to paralysis of the palate when aspiration into the trachea may occur. On examination the pupils are dilated, there is absence of the light reflex and nystagmus. The general muscular weakness is intense but there are no sensory disturbances and the reflexes are painless.

The systemic symptoms are subnormal temperature at first and bradycardia and then a tachycardia, dyspnoea and cyanosis due to respiratory paralysis which is the most common cause of death.

**Diagnosis**—The diagnosis of this disease rests upon the characteristic symptomatology and the occurrence of the disease in a number of persons who have consumed the same food. The absolute diagnosis rests solely upon the demonstration of the toxin by injection of tainted food into susceptible animals or the isolation of the organisms by suitable bacteriological methods. There should be little difficulty in differentiating it from food infection. On the other hand confusion may arise in distinguishing this condition from certain cases of encephalitis. In botulism there is no change in the cerebrospinal fluid, an important point in distinguishing it from cerebrospinal virus infections.

- Downs, A. W. and Liddy, N. B. The Influence of Barbitol Upon Cocaine Poisoning in the Rat *J Pharmacol & Exper Therap* 45 383 1932
- Eldredge, L. F. and Jaffer, C. I. Mercury Poisoning from the Use of Anti Fouling Paints *J Indust Hyg & Toxicol* 24 11 1941
- Hamilton, A. Industrial Poisons in the United States New York 1925 The Macmillan Co
- Hoffman, E. L. Deaths from Lead Poisoning U. S. Bureau of Labor Statistics Bull No 420 Feb 1927, p 45
- Kaplan, Abraham and Leveault, Gerald V. Methyl Alcohol Poisoning (Report of 4 Cases) *Can Med Bull* 44 1941
- Kellaway, C. H. Snake Venoms and Antitoxic Immunity The Mathison Lectures M. J. Australia 11, 1931
- Kelly, S. A. and Latham, H. J. V. The Treatment of Lead Poisoning by Sodium Citrate *Am J Med Sc* 206 404 1943
- Lambert, A. Treatment of Drug Addiction *J A M A* 96 823 1931
- Lambert, A. Intoxicants and Narcotics Nelson Loveleaf Living Medicine Nelson & Sons New York 1929
- Lambert, G. W. and Latterson, H. S. Poisoning by Mercuric Chloride and Its Treatment *Arch Int Med* 16 815 1915
- Lead Poisoning, Symposium *J Indust Hyg & Toxicol* 25 33 1943
- Le Clerc (de Saint Lo) - Le Petrole en ingestion Bull et mem Soc. med des hop de Paris 49 232 1925
- Light, A. B. Physiologic Aspects of Opium Addiction *J A M A* 96 823 1931
- Meyer, K. F. Newer Knowledge on Botulism and Muscel Poisoning *Am. J Pub Health* 21 712 1931
- Neel, Paul A. et al. Mercurialism and Its Control in the Felt Hat Industry *Pub Health Bull* 263 1941
- Noguchi, H. Snake Venoms an Investigation of Venomous Snakes With Special Reference to the Phenomena of Their Venoms Carnegie Institution of Washington 1909
- Vann, J. A. and Martin, E. M. Gasoline and Kerosene Poisoning in Children *J A. M. A* 103 42 1934
- Oliver, T. Lead Poisoning London 1914 H. K. Lewis & Co Ltd
- Pratt-Johnson, J. The Action of Petrol on the Central Nervous System *South African Rec* 24 543 1926
- Rambousek, J. Industrial Poisoning translated by T. M. Legge London 1913 Edward Arnold & Co p 144
- Rosenau, M. J. Preventive Medicine and Hygiene ed 5 New York 1927 D Appleton & Co
- Rosenthal, S. M. Mercury Poisoning *J A M A* 102 1273 1934
- Rothman, D. B. Alcohol in Special Disease *J A M A* 127 764 1945
- Savage, W. G. and White, P. B. An Investigation of the Salmonella Group With Special Reference to Food Poisoning Special Report Series 92 Medical Research Council Reports London 1925
- Seever, M. H. and Tatum, A. L. Chronic Experimental Barbitol Poisoning *J Pharmacol & Exper Therap* 42 217 1931
- Smith, Adelaide Ross. Benzol Poisoning—Delayed *J Indust Hyg & Toxicol* 27 118 1945
- Smith, M. I. and Elvove, E. Pharmacological and Chemical Studies of the Cause of So-called Ginger Paralysis *Pub Health Rep* 45 1703 1930
- Smith, M. I. et al. Pharmacological Action of Certain Phenol Esters With Special Reference to the Etiology of So-called Ginger Paralysis *Pub Health Rep* 45 2509 1930
- Stokes, J. H. Modern Clinical Syphilology Philadelphia 1926 W. B. Saunders Co p 281
- Tatum, A. I. The Present Status of the Barbiturate Problem *Physiol Rev* 19 42 1939
- Vogt, E. C. Roentgenologic Diagnosis of Lead Poisoning *J A M A* 98 125 1932
- Weiss, H. B. Mercuric Chloride Poisoning *Arch Int Med* 33 224 1924.

**Treatment**—As soon as a victim is bitten by a snake a tourniquet should be applied a few inches above the point of inoculation. Incisions in a cross or cross fashion through the skin with a knife or razor to open the fang punctures should be made. This will permit a forced suction by the mouth or by cups to promote a free flow of serum and lymph. If the edema should extend beyond the tourniquet, in addition one should be applied and incisions and suction used through the edematous area.

The patient should receive as soon as possible an injection of antivenum. The amount given will depend upon the amount of toxin inoculated which will be in proportion to the size of the snake. It should also be in direct proportion to the interval between the inoculation and the application of antivenum. There are three principal antivenums prepared in America at the present time. One is more or less specific against the copperhead, moccasin and rattlesnake while the other two are principally effective against the snakes of Central America. Unfortunately there are many varieties of rattlesnake, and therefore the antivenum is not as specific as could be desired. The injection should be repeated two or three times, particularly in small people and children as the toxicity of the venom is in reverse ratio to the body weight.

The infiltration of the tissues about the site of the inoculation with 1 per cent carbolic acid has been advocated. The results are most encouraging and it has a further advantage that carbolic acid is readily available under most circumstances. Alcohol has been a traditional remedy. There is no evidence that it is specific but rather that it acts as a sedative and a reassurance to combat the terror expected by the victim. Pain is usually severe and should be relieved by analgesics or sedatives. In collapse intravenous saline solutions and at times blood transfusions are indicated.

### References

- Allnutt, Samuel and Bowman, Karl M. The Effect of Liquid Gasoline on Pulmonary Tissue. *J. A. M. A.* 94: 100 (1930).
- Arnold, A. Animals Against the Snake. *Antivenum* (Philadelphia) 1: 11 (1931).
- Aub, J. C., Fairhall, L. T., Minor, A. S. and Koznikoff, I. Lead Poisoning. *Medicine* 4: 1 (1925).
- Battle, J. C. The Effect of Liquid Gasoline on Pulmonary Tissue. *J. A. M. A.* 94: 100 (1930).
- Bell, H. E. and Wilkins, M. A. F. *Armed Forces Selection of Cases for Army Medical Corps* 81: 11 (1931).
- Billow, Bennett W. Barbiturate Intoxication and Its Treatment. *Int. J. Anesth.* 29: 1 (1941).
- Brown, J. L. Benzene as a Hazard in Industry. *Brit. J. Hyg.* 7: 1 (1934).
- Council on Pharmacy and Chemistry. B.A. (Br. Anti-Lavender) in the Treatment of Arsenical and Mercurial Poisoning. *J. A. M. A.* 131: 26 (1941).
- Dickson, F. C. Botulism: a Clinical and Experimental Study. *Monographs of the Rockefeller Institute for Medical Research* 1918: No. 8.
- Dinberg, M. C. Benzol Poisoning. *Canad. M. A. J.* 3: 1 (1941).
- Ditmars, R. I. Snakes of the World. New York, 1941; The Macmillan Co.
- do Amaral, A. Poisonous Snakes and Treatment of Their Bites. *Southwestern Med.* 12: 100 (1928).

## 1.03

## 2

Abdominal ecchymosis in leishmaniasis 1458  
 crabs, in acid 1456  
     in acute mercury poisoning 149  
     in high barometric pressure 1456  
 purplish tinge in basophilic 597  
 Abnormal environment in insecticide 141  
 Abortion in undulant fever 694  
 Abscess alveolar bronchitis chronic 116  
     abscess 11  
     in crabs 61  
     brain bronchitis 15 16  
 bronchiectatic. See *Br. cicatricial* cat  
     lungs cysts 160  
 elephantiasis, 1340  
 extralungal spinal cord 1081  
 gastric 63  
     in acute glanders 1340  
     in appendicitis 656  
     in bronchiectasis 16  
     in bronchopneumonia  
     in chronic in umbilicus 64  
     in gonorrhea, 13 9  
     in erythema 6  
 intracranial 10 8 1081  
     in ribonin in appendicitis 66  
     in trichinosis 50 1  
 pulmonary in tuberculous 303  
 pyemic. See *Hejastis acuta suppurative*  
     38  
 tropharyngeal 9  
 subcutaneous in infusoria 111  
 Absorption intestinal diseases of 639  
 Accidental tortuosity psychomotor medicine  
     11 0  
 Acetylation sulfonamide 14 3  
 Achalasia. See *Esophagus dysphagia func-*  
     tional 59  
 Actinuria in pellagra 9  
     in strach acidosis 706  
     in subacute combined degeneration of spinal  
     cord 1129  
     in tropical sprue 543  
 Actinopteria 1 10 1 13  
 Actinoptera 669  
 Acid balance 86 864  
     equilibrium in epilepsy 1150  
 Acid decrease in secretion in gastric secretion  
     605  
 Acids 1 864 866  
     carbohydrate tolerance 833  
     carbon dioxide combining power of plasma  
     864  
 coma, differentiated from in ulnar coma 833  
     differentiated from acute in ribonin infec-  
     tions 833  
     in diabetes mellitus 83 848  
     in epilepsy 11 0 11 1  
     in metabolic alcohol intoxication 1480  
     in uremia 1 1  
     infection 834  
     muscle physiology 248  
     symptoms and signs 833  
     treatment 867  
 Acroasphyxia. See *Acrocyanosis* 46  
 Acrocephaly 1 7  
     cyanosis 46  
     differentiated from Raynaud's disease 46  
 Acetylation 94 95 109  
     differentiated from erythromelalgia 463  
 Acromegaly 893 896  
     differentiated from hyperkeratosis of the  
     skull 1227  
     from strach disease 1 6  
 Actinomyces 699  
     in lung 319  
     on tongue 40  
 Acute cor pulmonale 359  
     pneumonia. See *Pneumonia primary*  
     atypical 2 5  
     rheumatic fever sulfanilamide in prevention of  
     of 68  
     in water. See *Liver: acute yellow*  
     atrophy 741  
 Alantoin 1129  
 Alantoin syndrome. See *St. Les. Ad.*  
     syndrome 397  
 Adaptation and name 1200

All on Bler = in mla See Pernicious  
     are ia 3  
 All onian an mia See Pernicious a iem a  
     53  
 Addison's di = 934 240  
     crisis 93  
 Alentia See al o suckling of glands  
 cervic l differentiated from mumps 97  
     in acute tonsillitis 1  
     in diphtheria 83  
     in mea li 101  
     in rub lla 10  
     in scarlet fever 6  
     in tularemia 1336  
     in whooping cough 127  
 Alknol i cations 31 53  
     differentiated from nasopharyngeal  
         fibr ma 32  
     mouth breathing 31  
     symptoms 21  
 Alenolipomatoses 883  
 Alenoma in acromegaly 893  
     lands of Langerhans ?  
     pituitary 11 8  
     sebaceum in tubero = sclerosis 1040  
 Alenopathy 58  
     cervical See Lymph glands enia ge nent  
     in chronic tonsillitis 4  
     in lymphopathia ne cum 1398  
     in serum di ea 1438  
     in smallpox 139  
     mononuc o l acute 140 1403  
     regional in tularemia 1337  
 All ions subarachnoid cnephalography  
     1032  
 Alheave pericarditis 359  
 Aldie syndrome 104 1054  
 Aldipos dolorosa 883  
 Aldipos cerebri 883  
     ality of trunk in ba ophil m ■  
 Aldrenal cortex emotional factor 1 00  
     tumor See Suprarenal glands tumors  
         cortical 941  
     cortical function acute in efficiency 933  
     glands atrophy in Addison's disease 934  
     function 130  
     tuberculo is of in Addison's disea e 934  
         936  
     in efficiency in cardiac failure progres ive  
         congestive 3 7  
 Aldrenalin 888 930  
     antagoni t to insulin 930  
     in ulin reaction 883  
 Aldrencort cal function direct methods 938  
     indirect metho d 83,  
     des troypti mo juto 736  
 Vegophny pl urat effu lcn 493  
 Verophag a in gastric neuro es 6 ■  
     affect equal al nt psychosomatic med cne  
         11 1  
 African sleeping sickn s 1289 1291  
     trypanosoma ls 1389  
     After damp 1460  
 Aggranulocyte angina See Ag annl cytois  
     564  
 Aggranulocyte 564 66  
     after an dopryne drug 64  
     ar en c pol oning 13 3  
     blood examinon 56  
     caused by sulfanilam le 64  
     different at d fr m aleucen c reticulo m  
         5 6  
     diphth ria ang na 88  
     follicular ton ill t s 51  
     in syph l 1323  
     in ulce ative infection of larynx 1 2  
     sulfonamide toxicity 14 5  
 Agraphia 1011  
 Ague See Mala al feve s 1366  
 Air hunger n ac du m 833 864  
 A illness compr ed 1457  
 Air sickne 1469  
 Alb ra Schonburg's d ase See Oste petro  
     at 1 17  
 Alb ghts yndrom See Fib ous dy plasia  
     1219  
 Albuminuria 125 1 9 1 82  
     in a ute follicular ton ill t s 51  
     in amylo d diseases of the dney 1283



## INDEX

- [illegible]

- Albuminuria—Cont 1  
   in chronic glomerulonephritis 1 66  
   in chronic hepatitis 746  
   in epidemic follicular tonsillitis 3  
   in glomerulonephritis 1 7  
   in infections of kidneys 1 89  
   in mu tarl gas poisoning 139  
   in nephritis 1 3 1 4  
   in scarlet fever 3  
   in yellow fever 13  
   orthotatic 1 8  
 Alcohol mal 60  
   methyl in acid 1 865  
 Alcoholic hallucinations acute 14 8  
   polynucleosis 1031  
   trance 14  
 Alcoholism acute 14 6  
   treatment 14  
   chronic 14  
   differentiated from beriberi 8  
 Aleppo boil See Oriental sore 1384  
   sore See Oriental sore 1384  
 Leukemic petechiae 6  
   toxic 1011  
 Alkaline phosphate tetany 964  
 Alkalosis 866 868  
   in cyanosis 189  
   in emphysema 99  
   in gallstones 11 0 31 1  
   in lobar pneumonia 3  
   in multiple sclerosis 348  
   tetany in 1 1 961 964  
 Alkaptonuria in chromasia 88  
 Allantasia 1498 1499  
 Allergic exanthema See Hay fever 144  
 Allergy 143 14  
   anaphylaxis 143  
   causes of 1441  
   clinical reactions 1441 1442  
   colitis ulcerative chronic non specific 701  
   definition 13  
   detection of 1447  
   epilepsy 1447  
   histamine test 1450  
   idiosyncrasy 143  
   immunity 143  
   intradermal test 1443  
   migraine 14  
   misallergic reaction 14  
   ophthalmic test 1443  
   patch test 1443  
   physiology 14  
   scratch test 1443  
   substances which may excite 144  
   test 1441  
 Allodermatitis inguinalis 136  
 Alopecia in congenital syphilis 1311 131  
 Alveolar emphysema symptom of 11  
 Alzheimer's disease 113  
 Amaurosis 998  
   in autotrophic family 1038  
   in congenital syphilis 1318  
 Amblyopia 948  
 Amebiasis differentiated from chronic 144  
   in tropical 144  
 Amebic abscess 39  
   of liver differentiated from malaria 137  
   dysentery See Dysentery amebic 640  
 Amerorrhea 9  
   in Simmonds' disease 901  
 American herpetosis See Espund 1386  
 Amnionitis 1468  
 Amyelia 1035  
 Amyloid disease in bronchiectasis 1  
   of kidney 1 33  
   spleen degeneration 3  
 Amyloidosis 304  
 Amyotonia congenita 104  
 Amyotrophic lateral sclerosis 1145 1147  
 Anabolic phase 78  
 Anal phase 33  
 Anaphylactic shock See Serum shock 1439  
 Anaphylaxis See Allergy 14  
   definition 143  
 Anastomosis in liver 18  
 Anatoxin 91  
 Anemia Addisonian 534  
   aplastic 546 549  
   differentiated from agranulocytosis 3  
   in arsenic poisoning 13 3  
   in benzene poisoning 146  
   in congenital syphilis 131  
   in syphilis 13 3  
 Anemia—Cont 1  
   bronchial obstruction symptoms 168  
   causes 1  
   chronic 144 14  
   color index 31 3  
   effects of radium and x ray 1471  
   erythrocytes in 1  
   hemolytic causes 1  
   sulfenamide toxicity 14  
   hyperbilirubinemia 5 1  
   hypochromic in cancer 1 stomach differ  
   entiated from pernicious anemia  
   43  
   in chronic hepatitis 746  
   in cirrhosis of liver differentiated from  
   pernicious anemia 543  
   in steptosis 1 18  
   in subacute lymphatic 143  
   microcytic 37 46  
   differential bothria 1 08  
   in chronic 144 641  
   differentiated from per  
   nicious anemia 43  
   in cell in ou lion 46  
   hypochromic 3  
   causes 36  
   chlorosis 30 33  
   chronic 144 14  
   differentiated from idiopathic  
   hypochromic anemia 534  
   differentiated from pernicious anemia  
   43  
   idiopathic 33 53  
   in cirrhosis of liver 641  
   in pregnancy 34  
   in scurvy 38  
   in splenic anemia 3  
   in subacute combined degeneration of  
   spinal cord 1139  
   microcytic 570 53  
   in ankytosis 1 04  
   nutrition 144 35 36  
   in acute leukemia 60 561  
   in bronchial obstruction 168  
   in cancer 3  
   in cardiac failure progressive congestive  
   3  
   in cholera 6 6  
   in chronic nephritis 3  
   in endocarditis bacterial subacute 409  
   in famulid purpura 5 3  
   in gastric function disturbance 3  
   in leukopenia 1 4 583  
   in leukemia 138  
   in liver cirrhosis splenomegaly 16  
   in lead poisoning 1488 1490  
   in leucemia 5  
   in liver disease 5 3  
   in lupus erythematosus disseminatus 141  
   in lymphatic venous 13 8  
   in nephritis treatment 1 80  
   in nutritional edema 163  
   in radiologic disease 14 1  
   in rat bite fever 1349  
   in regional ileitis 6 8  
   in rheumatic fever acute 5  
   in rheumatoid arthritis 1240  
   in scleroderma 11  
   in epithelium 1303  
   in syphilis 1304  
   in trichoccephalia 1 0  
   in tropical sprue 443  
   in tuberculo of lung 86  
   in uremia 1  
   microcytic See Anemia 144 144 5 3  
   nutritional 5 3  
   of pregnancy 34  
   differentiated from idiopathic hypo  
   chromic anemia 34  
   pernicious See Pernicious anemia 534  
   sickle cell See Sickle cell anemia 54 549  
   spherocytic See Jaundice hemolytic  
   chronic 549  
   splenic See Banti's disease 3  
   splenomegaly 33  
   symptoms 5 5  
   in on and Plummer's syndrome 533  
   anemia hyperchromic macrocytic 537 546  
   hypo chromic microcytic 530 53  
   Anencephaly 1035  
   Anesthesia in functional disorders of larynx  
   119  
   Anesthetic epilepsy 1406 1407  
   Anesthetic sudden death 353



Aneurysm aortic 43 44  
 abdominal 440  
     enlink 436  
     in 3 436  
     in c nlink 1 rtion March 438  
     in rtic e n rtic 439  
 differ ntial 1 fr m newgrowth s of  
     bron 11 1 0  
     in plagi 436 436  
     in d n thoracic 43  
     in paralys 1 r y n ad in 436  
     in ut tion 438  
     in sinu ca f v l diva 436  
     in phili 43 436  
     in trans r e arch trach al tucking 438  
     in x ray in 436  
 arteriovenous 44 311  
     coll i n g pul 443  
     hair in 413  
     in rt nlarge nent in 443  
     in thill in 443  
     in carinae in car nary artery 11 a 4 4 6  
     in rebal art ri s 462  
     in sign is 440  
     in li aceting 43 443  
     in larger arterie 440  
     in mycotic 43  
     in n row 3 ten vascular l stons 1111  
     in prino 1 441  
     in tr atm nt 441  
     in ntrial e in onary art ry M a en 4 6  
 Angina a n r nul cytic see 4 p an lo ptoov  
     164  
     in differ ntial 1 from blist r ia 88  
     in pikemic tript c c u see 70 ill i 1  
     in le o f the r r  
 in scarlet f ver 8 9 80  
 in uic raly stomatiti 4  
 Ludwig 4  
 of it 338  
 i ctoria 33  
     in r nary arterie in 4 3  
     in differential d from elokthil si 62  
     in e ot i nal f iet r s 118  
     in tle in acute l ue n 560  
 ulcerome n rous see 4 p iatit s i c e a  
     in 4  
 Vincent s see 1 p n e s angina 9  
 Angina of it 338  
 Angina a 11 9  
     in nervous syst m vascular r leal na 1111  
 Angiocarditic len 4 see 1 r i m 1444  
 Angi tonin 446  
 Angi r mi in a ido i 86  
 Angio lomia 1 r 04 v  
     in ino phic granu l i 110 1 in  
     in tropical s i r u s 643  
 Anorexia 598 619  
     in enoti nal fact r 1191  
     in n ac ic i 86  
     in m ac r d n l 94  
     in ch a 6  
     in r y pelias 130  
     in l y n phor atti v ner m 13 7  
     in trench f er 13 6  
     in t ut u g n u h i l e a m 12 4  
     in tub rculosis of lungs 33 9  
     in t yph id f er 661  
     in un lulant f er 393  
     in whoop n g cough 1 6  
     in n rve a 598 1194  
     in symptomatic 9  
     in tumor malignant 619  
 Anoxemia art rial in lung 178  
     in emphy ema 187  
     in loba pneum ia 35 52  
     in low baromet ic pressure 1459 1460  
     in myxedema 926  
     in respi atory fatigu 118  
 Anoxia lower nephron nephrosi 1 84  
 Anterior horn cells 983 986  
 Anthracosis 271  
 Anthrax 133 1339  
 Antibiotic therapy ind cations fo 1429 1431  
     in crequisite 1421  
 Antibiotics 1419  
     in chemothe apy 1419 1436  
     in bacter al ff ct 14 n  
     in mallpox prophylaxi 1432  
     in t xic effe t 14 5  
 Anti h tamine drug allergic r actions to  
     in insulin \$ 4  
     in asthma 1450  
 Antimony intoxicat on 739  
 Antitoxin diphtheria 20 92

[illegible]

- Arsenic poisoning.—Cont'd  
   hepatitis 13 2  
   Jarisch Herxheimer reaction 132  
   nitritoid crisis 132  
   sudden death 13 3  
   treatment 1495  
 Arsenical poisoning effect of lewisite 141  
 Ar enicals in relapsing fever 1361  
 Arphenamine in gangrenous stomatitis 47  
   in spiriochetal bronchitis acute 14  
   intoxication 739  
 Arterial thrombosis in typhus fever 13 3  
 Arteries cerebral 481  
   coronary 411  
   mesenteric 48  
   pulmonary 484  
 Arteriosclerosis 431 48  
   and hypercholesterolemia 539  
   chronic pulmonary 3 9  
   etiology 8 7  
   in diabetes mellitus 87 8 7 879  
   in nervous system vascular lesions 111  
   1115  
   in ochronosis 583  
   in osteitis deformans 1 74  
   in osteitis fibrosa cystica 96  
   paralysis agitans 1117  
   pathology 829  
 Arteriosclerotic valvular disease 48  
 Arthralgia in lupus erythematosus disseminatus 141  
 Arthritis See also Osteoarthritis 1 49  
   acute rheumatic fever 57 58  
   atrophic See Arthritis rheumatoid 1 38  
   chronic nonsuppurative 1 37  
   deformans See Arthritis rheumatoid 1 38  
   differentiated from erythema arthriticum 1413  
   degenerative See Osteoarthritis 1 49  
   differentiated from myxodema 9 6  
   exudative in lupus erythematosus disseminatus 1412  
   gonorrheal 1330  
   hypertrophic See Osteoarthritis 1 48  
   in amebic dysentery 6 0  
   in follicular tonsillitis 53  
   in glanders 1340  
   in influenza 111  
   in mumps 96  
   in Salmonella suispestifer infection 69  
   in scarlet fever 76  
   in serum disease 1438  
   in typhoid fever 685  
   infective See Arthritis septic 1336  
   acute in acute rheumatic fever 67  
   pneumococcal in rheumatic fever acute 67  
   proliferative See Arthritis rheumatoid 1 38  
   rheumatoid 1 38 1 49  
   anemia in 1240  
   diet in 1246  
   differentiated from gout 876 1 44 1 40  
   osteoarthritis 1244 1 46  
   rheumatic fever 1 44  
   drug therapy 1 48  
   emotional factors 1 01  
   etiology 1 38  
   fibroid nodules 1243  
   foci of infection in 1 38 1 40  
   joints in 1 40 1943  
   juvenile 67 1 4  
   Marie Strümpell type 1 41  
   physiotherapy 1 48  
   poker spine 1241  
   sawage like fingers 1 40  
   spondylitis in 1 41  
   Still's disease 1 42  
   streptococcal in 1238  
   symptoms 1240 1 43  
   treatment 1246 1 49  
   vaccines in 1 47  
   x ray findings 1 4  
   sciatica in 1149  
   senile or senescent 1 2  
   septic 1238  
   tuberculous in arthritis rheumatic acute 67  
 Arthrodysplasia hereditary of nails 1 28  
 Artificial pneumothorax See Pneumothorax artificial 1 8 54  
 Asbestos body in pneumoconiosis 271  
 Asbestosis 271  
 Ascariasis 0  
 Aschoff body in rheumatic fever 56  
   58 59 61 64  
 Ascites 508  
   in liver disease 17  
 Ascold reaction in anthrax 1339  
 Aspergilloma in lung 320  
 Splenomegaly differentiated from pleural anemia 533  
 Asphyxia in foreign bodies in bronchi 174  
   local See Cyanosis 460  
   traumatic 11  
 Astereognosis 1008  
   in parietal lobe tumors 1131  
 Asthenia in Addison's disease 930  
   in tuberculosis of lungs 303  
   neurocirculatory 313 1184  
 Asthma 144 14 0  
   antihistamine drugs 14 0  
   bronchial mediastinal emphysema acute 10  
   rises in 133  
   caused by sinusitis paranasal chronic exsiccated in 133 1447  
   differentiated from fibrinous bronchitis 144  
   emotional factors 1179  
   cosmohilia 77 1448  
   in chronic fibroclavate pulmonary tuberculosis 299  
   in pulmonary tuberculosis in 303  
   pulmonary pneumatocele 163  
   rises in 133  
   sputum in 1448  
 Astroblastoma 11  
 Astrocytes 9 8  
 Atocytosis 11 11  
 Ataxia cerebellar hereditary 1043  
   Friedreich's See Friedreich's ataxia 104  
   hereditary See Friedreich's ataxia 1042  
   in chorea 6  
   in general paresis 1056  
   in subacute combined degeneration of spinal cord 1139  
   in syphilis 131  
   in tabes dorsalis 10 8 10 9  
   Erlizaeus Verzbacher disease 1039  
   symptomatic 10  
 Atelectasis See Pulmonary atelectasis 199  
   acute massive See Pulmonary collapse acute massive 0  
   in new growth of bronchi 164  
   pulmonary in bronchopneumonia 10 290  
   signs in parenchyma of lungs 190  
 Atheroma coronary 48  
   in cardiac failure progressive congestive 3 8  
   of aorta 421  
   pulmonary aneurysms in 188  
   in chronic hyperemia 19  
 Athetosis 49  
   double 1041  
   in infantile cerebral palsy 1040  
 Atomic bomb injuries 147  
 Atony gastric 6 8  
 Atrophia Intoxication 39  
 Atrioventricular block dropped beats 393  
 Atrophy face in leprosy 140  
   in herpes zoster 1092  
   in myotonia atrophica 1047  
   in Werdnig Hoffman disease 1046  
   muscles in brachial plexus trauma 1099  
   ocular peroneal 10 0  
   myopathic See Dystrophies hereditary progressive muscular 1048  
   optic chiasm intracranial tumor 113  
   in acrocephaly 1 78  
   in epidemic cerebrospinal meningitis 1069  
   in hereditary cerebellar ataxia 1043  
   in intracranial tumors 11 4  
   in Pelizaeus Verzbacher disease 1039  
   in tabes dorsalis 1060  
   primary hereditary 10 1  
   progressive muscular 1145 See also M.J.  
   asthenia gravis 1143  
   aura in epilepsy 1151  
   in whooping cough 126  
 Actinomycin administration method and dosage 1429  
   chemotherapy 1420  
   curative value 1433 1436  
   in pneumonia atypical 6  
   in undulant fever 694  
   susceptibility of living organisms to 1431  
   toxic effects of 1476  
 Auricular fibrillation 39  
   coronary artery disease 476  
   in rheumatic fever acute 8



## Blue I—Cont 1

- glucose diabetes mellitus 518  
hyperbilirubinemia 51 41  
in lupus erythematosus disseminatus 141  
in urine 1 19  
leucocyte 7  
in bronchopneumonia 9  
lymphocytes 9  
monocytes 9  
nucleated red cells 37  
pho phates low in ecclae disea e 641  
platelets 527 66 74 See also Thromb  
cytopenia 5 9  
lecrease 1 570  
diseases of 566  
increased 4  
essential thrombophilia 574  
potassium labile com 533  
pressure 34 See also Hypertension 444  
also Hypotension 458  
disturbance 444 48  
low in malaria 92  
reticulocytes 9  
pitting symptomatic 10  
sugar curve diabetes mellitus 33  
diabetes mellitus 318 3 1 3 4  
in relation to liver function 1  
low cellae disea e 641  
vessels diseases of 4 9 367 31 3  
lymph nodes in dystonia musculorum de  
formans 1147  
Roos's sarcoma See Lymphogranuloma  
venereum 314 317  
Dons atrophy in syringomyelia 113  
cysts in 1 114 fibrous cysts 96  
disease hereditary 1 0  
mucus 0  
block platelet 7  
in chronic hemolytic jaundice 0  
in pernicious anemia 43  
in polycythemia vera 7  
Dons diseases of 1 05 1 8  
metabolic and developmental disorders  
1 09  
tumors classification 1 0  
fragility in osteoclasts imperfect 1 1  
1 16  
in dysplasia alveoli 1 0  
Bony defects in lipoid granulomatosis 9  
Boomerang skin in yaws 132  
Botulism 1488 1499  
Boubas See Lungs 13 4  
Bovine small See Intestines and 6 9  
Bowels emotional factors 1194  
Bradycardia (Rate forty to fifty)  
heart block 39  
in diphtheria 5  
in tetanus 13 4  
in typhoid fever 689 691  
in yellow fever 3  
psychosomatic medicine 1183  
sinus 386  
Brazilian leishmaniasis See Espundia 1387  
trypanosoma 1 See Chagasic disease 1314  
Break bone fever See Dengue 118  
Breath fetid in foot and mouth disease 1344  
in ulcerative stomatitis 43  
shortness of synovial membrane 8  
Bright's disease 176 See also Glomerulonephritis 1264  
acidosis in 866  
classification 1 6  
diet in 12 6  
etiology 1 63  
purpura in 567  
treatment 1 76  
Brill's disease See Typhus fever 13 1

## Bronchopneumonia 9

- Bronchitis of 13 1 5  
carcinoma 163 17 9  
differentiated from pulmonary tuberculosis 14 306  
cough in 116 13 16a  
exacerbations in 132  
differential diagnosis 1 0  
expectoration in 13  
foreign body in 1 5  
differentiated from acute maxillary  
pulmonary collapse 04  
differentiated from new growth in  
bronchus 1 1  
inflammation 1 0  
new growths 1 12 1  
anemia in 168  
bronchospasm 161  
clubbing of fingers in 168  
cough in 16  
cure and termination 1 1  
cyst in 16  
dermoid cyst 164  
diagnosis 1 0  
differentiated from bronchiectasis 1 0  
bronchitis chronic 148 1 0  
foreign bodies in bronchus 1 1  
purulent effusion 1 1  
tuberculous 1 0  
lymphatic in 167  
lymphoma in 165  
fever in 168  
infectious 167  
lymphatic glands enlarged 18 1 0  
metastatic tumors 164  
onset of 16  
orthopneumonia hypertrophic in 168  
in 16  
neuronal lesions 171  
neuronal lesions in 1 0  
sign 167  
sputum in 166  
treatment of 1  
tumors benign in chronic pneumonitis  
9  
unequal pupils in 16  
vocal cord paralysis in 16  
x-ray treatment 169  
leukocyte count of inflammation 141  
obstruction acute was the pulmonary col  
1 1 1 0  
leukoma 1 1  
rales in 133  
sarcosis 164  
symptoms 13  
terminal infection bronchitis 148  
tuberculous (differentiated from acute  
bronchitis) 145  
differentiated from chronic bronchitis 146  
in bronchiectasis 15  
tumors bronchogenic in 1  
metastatic 164  
microscopical examination 169  
Bronchial aneurysm See Aneurysm 149  
in thymus See Lymphoma 144  
distention See Bronchiectasis 149  
distraction cytolysis in 166  
Bronchiectasis 149 153  
abscess in 2 1 6  
acute 150  
atrophic disease 155  
bronchial exudate 152  
bronchopneumonia 1 0 1 5 1  
bronchocopy in 174 1  
cavitary abscess 114  
cyst 1  
cleftothorax in 158  
chronic 150  
differentiated from bronchitis 151  
clubbing of fingers and thumb symptom of  
1 5  
congenital 1 0  
constititional symptoms 1 1  
cough in 1 1 155  
cystic aneurysm 15  
diagnosis 149  
diagnosis 15  
Diaphragm plug 1 1  
differentiated from bronchiectasis 1 0  
chronic bronchitis 148  
of lung 162  
in pneumonia 2 6  
new growths of bronchus 1 0  
tuberculosis of bronchus 153

Dr n li 1 la—C 11  
 drainage by po f re 1  
 epithel 1 1 2  
 expect ratl n in, 1 1 1  
 fibro la 1 1  
 f r l n b l i s 1 0 1 2 1 4  
 inf cti n 1 2  
 cancer ne 1 6  
 f r l n a, 153 1 6  
 in d n i n un nls, 1 0 1 4  
 in chr nic tr nctis 14 145 149  
 i r n sal in itis  
 in u nlla, 64 66  
 in p r l n i r in un nls 1  
 in hyl rtr hile t e artr r tly 1  
 t n l b r r n u nta, 1  
 in 1 1 a, 161  
 in n w growth f bronchi 164 166  
 inf ction r c 1 1 f 1 6  
 inflammation r 1 1  
 infla nza in, 1 1 3  
 lik l i in 1 4 1  
 l bar in un nls 1 0  
 nann r c f nct, 1 1  
 m a l f c t r in 1 0 1 3  
 r nngitis in, 1  
 ustari g r 1 1 nng sympto f 133  
 n jla n in 1 6  
 n w r r w l 1  
 ct tract n, r n oval f 1 6  
 b ructi 1 0  
 paran sal nu tti chr ni in  
 f l i l i e 1 un t 1 1 0  
 in u n rax 1 9  
 ir d l i n g f r 1 1  
 pulm n r y inf cti n 1 0  
 pneu tuel 1 3  
 r ncti 1 1 n 1 4  
 f r 1 1  
 diff r ntial d from tuberc l in of lung  
 1 1  
 putum in 1 1  
 j n p l 1 1 1  
 c n titutional 1 1  
 j n n n 149  
 j p l l i in, 1 0  
 Traubesa plu 1 1  
 tr al nent, 1 6  
 tube cul al in, 1  
 ta c n 1 1  
 w l i n g c ch, fact r in 1 0 1 3  
 w r 1 2 1  
 B ncl i cti l e c r l l e i f f r ntiated fro  
 loc l i z 1 1 d r in umot rax, 162  
 localiz i n m tr ax, 162  
 lung c y t 163  
 I r n i l i e t l See B ch cta a 149  
 diff r nti l fr m f r n h cta 1 0  
 ng nital c y t s f lung a, 162  
 B m h i lectatic exiti a diff rent i 1 from  
 br n r nctal 163  
 loc l i z l i j r in umot rax, 162  
 localiz i n u thorax, 162  
 lung c y t 163  
 c y t i f f r ntial i from c y t s of lung 160  
 f r nchil i c a b e d y p n a, sympt m of  
 11  
 Dr n h i d i t i a See B onchopneumon a 14  
 i f f r ntial i f r a thma, 1445  
 in br ncl cta 1 1  
 in infla nza 119  
 in n u l 151  
 in rhin ti 1  
 r a l a in 132  
 u t c a t i a 111  
 Bronchiti acute See Tack B ch t s  
 ac i 134  
 in acute rhinitis 1  
 in ch onic bronchiti 146  
 rates in, 133  
 re piratory g n po soning 13 1 3  
 capillary See L on h p n e n o a 14  
 chr nic 14 142  
 abace a al colar 146  
 B cillus m l i 14 145  
 fu formia, 14 149  
 bronchiectasia in, 14 145 149  
 B onchitis acute factor in 146  
 bron hopneumon a in, 145  
 cardiac fallu e 145  
 causati e agent, 14  
 cau ed by chronic parana al m n u ti  
 common cold in, 146 145

Dr ncl i s i nle—Cont d  
 cough in 145  
 cour anit rination 148  
 cyan i 145 149  
 W gn is 145  
 i f f r ntial i f r m br nchil foreign  
 b l i inf cti n 1  
 i r ncl i tubercu la, 145  
 br n l i c t l 145  
 n w growth f r ncl i, 145 1 6  
 in u ncl i 145  
 puli n r y tubercu la 266  
 begn a in 145 149  
 n i l y n in 145 1  
 f r l g n l i s in 145 1 1  
 f r i d l n r c bacillus in 14  
 f n l y t i c indu nax 14  
 f n r r l c o l n, 14  
 in chronic i rana al indu itl  
 inf cti n in inu w rana al, 146  
 t r n i n d br n h i 146  
 in lu nza in 146 145  
 laryngiti in, 144  
 l i p l i in 146 146  
 m l a in 146 144  
 r bran us et rati in 146  
 M r c o r u s c t r r l l i 14  
 r u t i infecti m in 146  
 m a l c t a r t h f c t r of 148  
 m w growth 145  
 i u l g l e i n a t 1 14  
 in u n c c c l in 14  
 encum a n i in 146  
 p r i n i n l o t a r fact r c f 148  
 p r l i r n fact r n inf cti n a 14 14  
 puli n r y c n t i n, chronic in, 14  
 p r l e n c c i in 14  
 r o r r c a 146  
 r a l a in 145  
 Spiroch t r br nchil l i s in, 14  
 putum in 1 145  
 j n p t m a l n 145  
 s y n o n 14  
 t r in i infecti n 146  
 t r ncl i in 146 148  
 tratin nt, 149  
 tubercu la in 148  
 Vincent a spirillum in, 14 145  
 v l a p i n g c g in, 146 145  
 c y n i in 145  
 i f f r nt at i from asth n a 1449  
 f t i l i 1  
 n l i n u 143 144  
 Crare (L) i n crystals 144  
 in acut e r o c t a l f e p a t i t i 1  
 in l i n e n a 149 141  
 n l b r p n u nia, 29  
 in l y n t c y t o c r i n n i n g i t i a, 140  
 in m l c 100  
 in m u l t i l n c y t o m a, 1  
 in m u m f 36  
 in m u t a r i g r a t n i n g 138  
 in n w growth f bronchi 166  
 in tubercu l o f lung 59  
 n t y l h l i f c r 642 642  
 in t y l h u f e 18 3  
 in w l o p l i n g cough 1  
 recur n g f o n c h t u c h o c 14  
 sicc a d i f f r n t i l f r o m bronchiectasia  
 i n i c 1 1  
 p i r c i t e t a l a c u t e 144  
 i f f r n t i a l h g n o i 14  
 B onchog n e a c i n o m a i f f r n t i a t f r o m  
 c h r o n i c p n u m o n i t 9  
 in h o n l e i n u o n i t 9  
 n l i a t i n a c h n a 14  
 l u n k a c y s t a 161  
 Bronch p n u m o l a 14 1  
 abace a  
 a t l c t a 19 1  
 Bacillu pastis in 14  
 blood changes in 0  
 causati m agent, 14  
 circulat r y fallur in 18  
 ough in 16 3  
 ourse and termin t i m 1  
 cyanosis in 134 18 1 18 3  
 d g n o l 0  
 different at d f o m acute laryng tract o  
 bronchiti 13  
 i f f r n t i o l f r o m influenza, 111  
 d i f f e r e n t a t f o m l u b a r p n e u m o n i a 0  
 4

## Index—Cont.

- glucose diabetes mellitus 818  
 hyperbilirubinemia 51 41  
 in lupus erythematosus disseminatus 141.  
 in urine 1 9  
 leukocytes 7  
 in bronchopneumonia 20  
 lymphocytes 529  
 monocytes 9  
 nucleated red cells 57  
 phagocytes low in cellae disease 641  
 platelets 7 66 74 See also Thrombocytopenia 510  
   decreased 50  
   diseases of 566  
   increased 74  
   essential thrombophilia 574  
 potassium dihydrogen phosphate 833  
 pressure 34 See also Hypertension 441  
   also Hypotension 43  
 disturbances 44 48  
 low in scleroderma 132  
 reticulocytes  
   pitting symptomatic 10  
   scurvy 418  
   diabetes mellitus 818 819 84  
   in relation to liver function 1  
   low cell count 641  
 ventral torsion of 4 9 48 119  
 Body torsion in dystonia musculorum deformans 1147  
 Boeck's sarcoid 5 6 Lymphogranuloma venereum 314 317  
 Bone atrophy in syringomyelia 1137  
   cysts in osteitis fibrosa cystica 96  
   diseases hereditary 10  
   marrow 50  
   blood platelets  
     in chronic hemolytic jaundice 9  
     in pernicious anemia 543  
     in polycythemia vera 55  
 Bones diseases of 105 18  
   metabolic and developmental disorders 109  
   tumors classification 105  
   fragility in osteogenesis imperfecta 11  
   in dysplasia fibrosa 10  
 Bony defects in lipid granulomatosis 59  
 Boomerang shin in jaws 130  
 Botulism 1493 1499  
 Bouba See Lassa 1394  
 Bowel small See Intestines small 69  
 Bowels emotional factors 2194  
 Bradycardia (late forty to fifty)  
   heart block 397  
   in diphtheria 11  
   in tsutsugamushi disease 134  
   in typhoid fever 580 681  
   in yellow fever 3  
   psychosomatic medicine 1183  
   sinus 386  
 Bradypnea 330  
 Brain abscess in bronchiectasis 1 16  
   anatomy 48  
   blood supply 981  
   changes in general parasympathetic 110  
   cicatrical epilepsy in 110  
   edema of in cerebral contusion 110  
   gumma 106  
   tumors See Intracranial tumors and Intraspinal tumors 113 1134  
     differentiated from chronic adhesions  
     arachnoiditis 1078  
     from lead encephalopathy 1140  
   epilepsy in 1150  
   in diabetes insipidus 868  
   in hydrocephalus 1123  
   x-ray 1033  
 Brazilian leishmaniasis See B. braziliensis 1386  
 trypanosomiasis See Chagas disease 1391  
 Break bone fever See Dengue 138  
 Breath fetid in foot and mouth disease 1344  
   in ulcerative stomatitis 43  
   shortness of symptomatic 8  
 Bright's disease 16 See also Glomerulonephritis 1264  
   acidosis in 866  
   classification 16  
   diet in 11  
   etiology 163  
   purpura in 567  
   treatment 16  
 Brill's disease See Typhus fever 1251  
 Bromosulfalein 19  
 Bronchi diseases of 13 1  
   carcinoma 164 179 9  
   differentiated from pulmonary tuberculosis 106  
   cough in 116 13 16  
   epithelial in 132  
   differentiated from 170  
   expectoration in 13  
   foreign body 171  
   differentiated from acute massive pulmonary collapse 84  
   differentiated from new growth in bronchi 11  
   inflammatory lesions 10  
   new growths 173 1  
   anemia in 168  
   bronchus in 16  
   clubbing of fingers in 168  
   cough in 16  
   course of termination 11  
   cyanosis in 168  
   fistula 164  
   diagnosis 10  
   differentiated from bronchiectasis 10  
   bronchitis chronic 148 149  
   foreign bodies in bronchi 11  
   pleural effusion 11  
   tuberculosis lungs 10  
   asthma in 16  
   asthma in 16  
   scurvy in 168  
   inspection 167  
   lymphatic glands enlargement 16 10  
   metastatic tumor 164  
   necrosis 16  
   occur in pathologic hypertrophy in 168  
   pain in 16  
   pleural lesions 11  
   pre-urethral lesions 10  
   signs 167  
   putum in 166  
   symptoms of 1  
   tumors benign in chronic pneumonia 9  
   unequal pupils in 167  
   vocal cord paralysis in 167  
   x-ray treatment 169  
 Low rate cause of inflammation 141  
 Destruction acute massive pulmonary collapse 0  
   leucocytes 11  
   rashes in 113  
   sarcoid 164  
   symptoms 13  
   terminal infection by necrosis 148  
 Tuberculosis  
   differentiated from acute  
   pyothorax bronchitis 145  
   differentiated from chronic bronchitis 148  
   in bronchiectasis 15  
   tumors bronchoscope in 1  
   metastatic 164  
   microscopical examination 169  
 Bronchial aneurysm See Bronchiectasis 149  
   asthma See Asthma 1447  
   dilatation See Bronchiectasis 149  
   obstruction cyanosis in 186  
 Bronchiectasis 148 153  
   abscess in 1 16  
   acute 10  
   amyloid disease 1  
   bronchial exudate 15  
   bronchopneumonia 150 15 1  
   bronchoconstriction in 14 1  
   causative agent 119  
   cavity 11  
   chemotherapy in 158  
   chronic 150  
   differentiated from bronchiectasis 151  
   clubbing of fingers and toes symptom of 1 15  
   congenital 150  
   constitutional symptom 11  
   cough in 151 1  
   course and termination 15  
   dilatation 149  
   leucocytes 155  
   diet in 151  
   differentiated from bronchiectasis 10  
   chronic bronchitis 145  
   cysts of lung 153  
   pneumonia 26  
   new growths of bronchi 10  
   tuberculosis of bronchi 159

Bronchial —Cont'd  
 drainage by po tube 1  
 emphysema in 153  
 expectoration in 151 155  
 fibro 14 13  
 foreign bodies 150 13 14  
 inf cti na 13  
 gangrene 16  
 leiorrh 151 16  
 in bronchopneumonia 10 1 4  
 in chronic bronchitis 12 148 148  
 intranasal sinusitis  
 pneumonia 64 66  
 in Friedländer pneumonia 1  
 in hyperthymic osteoarthritis 1  
 in lobar pneumonia 47  
 in measles 101  
 in new growths of bronchi 164 166  
 infection re oval of 16  
 inflammatory 150  
 influenza in 150 153  
 isolated in 154 155  
 lobar pneumonia 10  
 manner of onset 11  
 measles fact r in 10 13  
 meningitis in 1  
 metastasis piling sympt 139  
 neoplasms in 156  
 new growths 1  
 obstruction removal of 156  
 obstructive 10  
 paranasal sinusitis chronic in  
 pathological anatomy 10  
 pneumothorax 19  
 predilecting factor 150  
 pulmonary infection 10  
 pneumonia 13  
 secondary lesion 1  
 scar 151  
 differentiated from tuberculosis of lung  
 151  
 putum in 11  
 symptoms 151 155  
 constitutional 12  
 synonym 149  
 tracheitis in 150  
 Traube's plug 11  
 treatment 156  
 tuberculois in 13  
 vaccine 158  
 whooping cough factor in 150 13  
 x-ray 13 15  
 Bronchiectatic cavities differentiated from  
 bronchiectasis 163  
 localized hydrothorax 163  
 loc. in lobar pneumonia 163  
 lung cyst 163  
 Bronchiectatic cavities differentiated from  
 bronchiectasis 163  
 localized hydrothorax 163  
 localized pneumothorax 163  
 lung cyst 163  
 cysts differentiated from cysts of lung 160  
 Bronchiole 117  
 Bronchiolitis 24  
 differentiated from a thymoma 2449  
 in bronchiectasis 159  
 in influenza 109  
 in measles 101  
 in rhinitis 21  
 rales in 123  
 suffocative 111  
 Bronchitis acute See Tracheobronchitis  
 acute 134  
 in acute rhinitis 1  
 in chronic bronchitis 146  
 ale in 13  
 expiratory gas polysmng 12 138  
 capilla 14  
 capilla 14  
 chest 14 149  
 abscess alveolar 146  
 Bacillus coli 145 146  
 fuiformis 14 148  
 bronchiectasis in 14 148 149  
 bronchitis acute factor in 146  
 bronchopneumonia 148  
 cardiac failure 148  
 causative agent 14  
 caused by bronchopneumonia 148  
 common cold in 146 148

Bronchitis chronic—Cont'd  
 cough in 148  
 course and termination 148  
 cyano 148 149  
 diagnosis 148  
 differentiated from bronchiectasis foreign  
 bodies infection 15  
 bronchiectasis 148  
 bronchiectasis 148  
 new growths of bronchi 148 176  
 pneumoconiosis 148  
 pulmonary tuberculosis 148  
 dyspnea in 148 149  
 emphysema in 148 1  
 foreign bodies in 148 1  
 Friedländer bacillus in 14  
 hemolytic influenza 145  
 hemorrhage in 147  
 in chronic paranasal sinusitis 2  
 infection in acute paranasal 146  
 terminal bronchi 146  
 influenza in 148 148  
 laryngitis in 148  
 lipulot in 148 148  
 metastasis in 148 148  
 membranous stomatitis in 146  
 Micrococcus catarrhal 14  
 mouth infection in 146  
 nasal catarrh factor of 148  
 new growth 148  
 pathological anatomy 147  
 pneumococci in 14  
 pneumoconiosis in 148  
 pneumonia lobar factor 148  
 predisposing factors infections 14 147  
 pulmonary excretion chronic in 147  
 pyogenic cocci in 148  
 pneumonia 146  
 rales in 146  
 Spirochetes bronchialis in 14  
 putum in 14 148  
 symptoms in 148  
 synonym 14  
 terminal infection 146  
 tonsillitis in 146 148  
 treatment 149  
 tuberculois in 148  
 Vincent's pyorrhea in 14 148  
 whooping cough in 146 148  
 cyano is in 152  
 differentiated from a thymoma 1449  
 follicle 151  
 fibrous 143 144  
 Cystic Leyden crystals 144  
 acute pyroclastic hepatitis  
 influenza 109 111  
 in lobar pneumonia 239  
 in lymphatic chorioiditis 140  
 in measles 109  
 in multiple myeloma 107  
 in mumps 96  
 in metastasis poisoning 138  
 in new growths of bronchi 166  
 in tuberculois of lung 89  
 in typhoid fever 681 682  
 in typhoid fever 13 3  
 in whooping cough 17  
 squamous cell bronchitis chronic 14  
 loca differentiated from bronchiectasis  
 chronic 151  
 differentiated diagnosis 14  
 Bronchiogenic carcinoma differentiated from  
 chronic pneumonia 259  
 in adenocarcinoma 14  
 lung cyst 161  
 Bronchopneumonia 14 3  
 abscess 2  
 atelectasis 19 21  
 Bacillus pestis in 14  
 blood change in 0  
 causative agent 14  
 expiratory gas in 18  
 cough in 15 2 35  
 course and termination 1  
 cyanosis in 14 185 17 18 3  
 diagnosis 0  
 differentiated from acute laryngotracheo  
 bronchitis 137  
 differentiated from influenza 111  
 differentiated from lobar pneumonia 0

## Bronchopneumonia—Cont 1

- dyspnea 16 73  
fever in 0  
Friedländer's bacillus 1 218  
gangrene 2 0  
hemolytic influenzæ 14  
in bronchiectasis 1 0 1-5 71  
in children 20  
in chronic bronchitis 148  
pneumonitis, 57  
in follicular tonsillitis 3  
in influenza, 109 111  
in lymphocytic chorionmeningitis 140  
in measles 101  
in mustard gas poisoning, 138  
in rhinitis acute 71  
in trichobronchitis acute 136  
in typhus fever 13-3  
in whooping cough 1 7 1 9  
intrapulmonary collapse 00  
lethal cause of 141  
manner of onset 15  
pathological anatomy 19  
phthisis *See* *Phthisis bronchopneumonia*  
form 39  
pneumococcus cause of 14  
prodromal factors 15  
pulmonary pneumococci 163  
rules in 133 218  
secondary lesion 19  
Streptococcus hemolyticus 14 19  
symptoms and signs 15 18  
synonyms 14  
treatment -  
Bronchoscopy in acute massive pulmonary  
collapse 63  
in bronchiectasis of 169  
foreign bodies 17  
new growths of 167  
in bronchiectasis 1-4 3-  
in chronic pneumonitis 268  
in fibrinous bronchitis 144  
in tumors of bronchi 17-  
Bronze diabetes *See* *Hemochromatosis* 0  
884  
Brown atrophy heart 407  
Brown Séquard paralysis 1018  
in extramedullary tumors 1134  
Brucellæ *See* *Undulant fever* 698  
Brudzinski sign leptomeningitis 106  
Lubomir plague differentiated from lympho  
pathia venereum 13 8  
Buccal irritating lesions 46  
Buerger's disease *See* *Thromboangiitis obli  
tans* 466  
Bulbar palsy 1006  
paralysis *See* *Flaccid bulbar paralysis*  
1146  
Bullmia in latent neurosis 627  
Bullia fever 1364  
Bundula branch block 298  
Bura 11 1364  
Burning sensation hands feet and mouth in  
foot and mouth disease 1344  
Burns in mustard gas poisoning 138  
in peripheral circulatory failure 3 1  
Bursitis 1 34 123

## C

- Cachexia malignant 1  
progressive 497  
strumipriva 9 6  
Calcitonin *See* *Baron's tripe pressure*  
high effects of 1457  
Calcium biliary calculi 365  
calculi in osteitis fibrosa cystica 96  
low blood 963  
metabolism 960  
renal calculi 965  
Calcium biliary calculi 965  
calcium in osteitis fibrosa cystica 96  
pancreatic 96  
renal 96 1 9  
rheumatic cause of parotitis chronic 47  
Camp fever *See* *Typhus fever* 1351  
Cancer *See* *Carcinoma*  
Carcinoma *See* *Parotitis glandularis* 45  
Cannabis indica 148  
Capillary blood flow in the liver 119-121  
engorgement in cyanosis 18  
pulse in circulatory diseases 331  
Caput Medusæ 146

- Cerebral sickle 1469  
Carbhydrate and fat metabolism in diabetes  
mellitus 8 1  
analogous metabolism in diabetes mellitus  
8 3  
tolerance in diabetes mellitus 840  
increased in Fröhlich's syndrome 89  
Carbolic acid poisoning in ochronosis 88  
Carbon monoxide poisoning 1464 1466  
Carbuncle diabetes 849 8 0  
of lips 3  
Carcinoma, anemia and 23  
bile ducts 771  
biliary tract, differentiated from acute in  
fectious hepatitis 34  
bronchi *See* *Bronchi new growths carci  
noma* 164  
bronchogenic. *See* *Bronchogenic carcinoma*  
5  
diverticulum in diverticulosis 667  
esophagus 1 1 96  
gallbladder 768  
large intestine 664  
larynx 132  
differentiated from syphilis 131  
differentiated from tuberculosis 199  
nose 6  
pancreas 11  
pharynx 30  
rectum differentiated from chronic hepatic  
114 749  
stomach 618  
differentiated from chronic hepatitis 44  
symptomatic 1  
thyroid gland 97  
radioactive iodine in 9  
tongue 40  
differentiated from syphilis 39  
differentiated from tuberculosis 40  
ventricular hyperchromic anemia in 46  
Circulation. *See* *Circulatory system dis  
eases* 11 10 Heart  
arterial 3-1 3 1 *See* also *Sudden death* 351  
treatment, 3 3  
ventricular fibrillation 3 1  
arrhythmias *See* *Arrhythmic disturbances*  
64 406  
compensation differentiated from ex  
ophthalmic goiter 917  
disturbance in acute wet beriberi 87  
diaphragm muscle physiology in 3 0  
esophageal 423  
vitamin B deficiency 351  
enlargement in valvulitis 382  
extra-vascular in diphtheria, 8  
failure 344  
acute in acute wet beriberi 8  
congestive 3 1 375  
acute 355  
in jaundice 3-3  
valvulitis 359  
arrhythmia 359  
diagnosis 3 3  
differentiated from beriberi 88  
digitalis 364 36  
duration 36  
in chronic fibrocystic pulmonary  
tuberculosis is 297  
in essential hypertension 4 1  
in fibroid tuberculosis 303  
infectious 356  
metabolic and nutritional disorder 357  
miscellaneous 358  
cyanosis 366  
pregnancy 369  
prognosis 360  
progressive 3 4  
infection 356  
metabolic disorder 357  
nutritional disorder 35  
vascular lesion 3 8  
trochanteric 366  
treatment 363  
valvulitis 359  
vascular lesion 358  
venous pulse 768  
in beriberi 788  
in chronic bronchitis, 148  
fibrocystic pulmonary tuberculosis  
10 18 297  
in emphysema 214  
in pneumoconiosis 2 3  
in whooping cough 127  
ventilation in 368



- Cudlar—C ut 1  
hypertrophy in sickle cell anemia 54  
leukons congenital 1 meglobin reduced 181  
in acute rheumatic fever 69  
rheumatoid 1183  
pain 336  
rhythm 164
- Cardiospasm See Esophagus dysphagia  
function of 9  
emotional factors 1193
- Cardiovascular collapse in typhus fever 13  
disease and diabetes mellitus 82 824  
system in lupus erythematosus disseminata 12 1112
- in rheumatic fever 67  
rheumatic nodules and 1180
- Carditis rheumatic fever acute 69  
Löffler's dental 41
- Carotid body 963  
disease of 963 9 1  
physiology 9 0  
tumors 9 1  
glands 963  
anus 969  
in epilepsy 11 1
- Carriers in ambly dysentery 6 1  
in cholera 6  
in diphtheria 83 89  
in meningitis epidemica 106  
in erythema 1  
in typhoid fever 686 691
- Casts in fibrinous bronchitis 143 144  
in intestinal mucous colitis 65  
in urinary nephritis 1 65
- Catabolic phase of injury 37  
Lutalyse in narcolepsy 11 6
- Cataracts in diabetes mellitus 85  
in myotonia atrophica 1048  
parathyroid 984
- Catarth See also Suffragato trinitra 184  
186  
nasopharyngeal in whooping cough symptoms of 1  
pulmonary suffragato See Bronchopneumonia 14
- Cauda equina lesion tumors 113
- Cavalgia 1110
- Cecitis See Appendicitis acute 6 4
- Cecum See Intestines in pt 646
- Celiac disease 641  
anemia in 641  
hypochromic anemia in 66  
intolerance of carbohydrates 642  
symptoms 641
- Cellulitis in scarlet fever 6  
in tularemia 1338
- Cerebellar atrophy in acute anterior poliomyelitis 1001
- Cerebellum disturbance of motility 999  
tumors 1183
- Cerebral arteries 481  
congestion 1101  
contusion 1109  
correlation of 9 3 9 9  
disease in nervous system 1006  
disturbance 115  
hemorrhage See Hemorrhage cerebri  
lesion 110  
thrombosis See Thrombosis cerebral  
tumor in epilepsy 11 2  
in calcareous 1110 1116
- Cerebro spinal fluid differentiated from  
Rocky Mountain fever 1 58  
in typhus 35  
fluid 10 4 10 8  
intracranial pressure 10 3  
complete block 10 1  
for nation 10 4  
in acute anterior poliomyelitis 1090  
in poliomyelitis meninges 10 7  
in atypical pneumonia 1399  
in birth 1097  
in cerebral vascular disease 111  
in epidemic cerebrospinal meningitis 1076  
in poliomyelitis 1087  
in equine encephalitis 1087  
in general paresis 1056  
in hydrocephalus 1113 1121  
in intracranial abscess 1079  
trauma 1193  
in tetanus 104  
in typhoid 11 chorion meningitis 1401  
in meningovascular syphilis 1053  
in multiple sclerosis 1142
- Cerebro spinal fluid—C ut d  
in meningitis 1088  
in pneumococcal meningitis 10 4  
in serous meningitis 10  
in spinal cord trauma 110  
in subarachnoid hemorrhage 110  
in syphilis of nervous system 10 1  
in tabes dorsalis 1062  
in tuberculous meningitis 10 3  
lumbar puncture 10 5  
pressure 10 1  
Queckenstedt's test 1026 1025  
ventricular puncture 1075  
meningitis See Meningitis epidemic cere  
bro spinal 1066  
syphilis 100 1051 105 10 5  
virus infection differentiated from botu  
lism 1438
- Cervical rib inequality of pulse volume 1110  
symptoms 1110  
vasomotor changes 1110
- vertebrae tuberculous caries in retro  
pharyngeal abscess 9
- Cestode infections 96  
Chaddock reflex 98
- Chagas disease 1391 139  
Chalky bones See Osteopetrosis 1 17
- Chancres differentiated from carcinoma of  
the pharynx 31  
in syphilis 1309 131 1318  
redness in syphilis 1304
- Chancroles differentiated from lymphoplasia  
venereum 13 8
- Charbon See Anthrax 1287
- Charcot-Leyden crystals 144 6 1445 See  
also Mucous colitis 65  
in eosinophilic leucemia 964
- Charcot-Mari Tooth atrophy See Visceral  
atrophy peroneal 1050
- Charco's joints in syphilis 181  
in syngonella 1137  
in tabes dorsalis 1060  
trial symptom in multiple sclerosis 1110
- Chelitis diffusa in syphilis 132
- Chemical intoxications 39 9 also Liver  
acute yellow atrophy 741
- Chemicals in diseases due to 14 6  
in moth (raps) administration method and  
dose of drug 14 6 14 9  
and antibiotic 1419 1430  
definition 1419  
in bronchiectasis 158  
in epistaxis 1304  
indications for 14 9 1431  
preparation 14 3  
toxic effect 14 4
- Chester's syndrome 3 0  
in chronic glomerulonephritis 1271
- Chickenpox 1249 1400  
differentiated from smallpox 1246  
herpes zoster 109 1 99
- Chills and fever See also Malarial fever  
1366  
focal infection 13  
in acute follicular tonsillitis 61  
mononucleosis 140  
in disease of bronchi 183  
in influenza 109  
in mumps 95  
in new growths of bronchi 168  
in papistat fever 138  
in plague 136  
in psittacosis 4  
in Q fever 1364  
in relapsing fever 1363  
in Rocky Mountain spotted fever 1 7  
in epidemic 1303  
in smallpox 1293  
in trench fever 13 6  
in tsutsugamushi disease 1354  
in tularemia 1235 12 8  
in typhus fever 1  
symptomatic 124
- Chin c 124 See Nitrofurantoin 124
- Chlorides absorbed in lower pneumonia 37 41
- Chloroform intoxication 39  
chloroma See Leucemia acute 61  
differentiated from multiple myeloma 1208
- Chloroquine in the oil rupt 14 0  
in syphilis 13 2  
in typhus 130 523
- Chloro See Ametua hypochlorite  
patite 523





Cough brass 436  
 bronchopneumonia in measles 101  
 croup in laryngeal diphtheria 85  
 emotional factors 1378  
 in acute laryngotracheobronchitis 13  
 massive pulmonary collapse 204  
 rhinitis 21  
 tracheobronchitis 13  
 in aortic aneurysm 436  
 in bronchiectasis 131 1 5  
 in bronchopneumonia 216 2 3  
 in chronic bronchitis 14  
 fibrovascular pulmonary tuberculosis  
 36  
 pneumonia 7  
 in circulatory diseases 193 331  
 in diphtheria 8 87  
 in diseases of bronchi 116 13 16  
 of larynx 126 1 3  
 of mediastinum 509  
 of trachea 116 139  
 in emphysema 1  
 in fibrinous bronchitis 233  
 in foreign bodies of bronchi 1 3  
 in Friedländer's pneumonia 3  
 in influenza 109  
 in kala azar 1388  
 in laryngotracheobronchitis acute 13  
 in lipid pneumonia 13  
 in measles 101 104  
 in new growths of bronchi 16  
 in pulmonary infarction 196  
 in Q fever 1364  
 in respiratory diseases 228  
 in tracheobronchitis 135  
 in tuberculosis of larynx 139  
 of lungs 28  
 in ulcerative stomatitis 43  
 in whooping cough 1 4 1 5 1 6 1 4  
 paroxysmal in new growths of bronchi 16  
 symptomatic 10  
 Countertransference in psychosomatic medicine 117  
 Cramps abdominal in acidosis 86  
 in acute mercury poisoning 1422  
 in high barometric pressure 14 8  
 heat 145  
 muscle in cholera 6 6  
 Cranial nerves 996 1006  
 operations in serous meningitis 10  
 trauma in chronic meningitis 10 7  
 Craniopharyngioma intracranial tumors  
 31 9  
 pituitary gland 904 90  
 tumors symptoms and signs 94  
 Craniotomy in chronic adhesive arachnoid  
 101 1078  
 Cranium bifidum 1038  
 Crepitation in trachea and bronchi disease  
 133  
 Cretinism 9 7 9 9  
 differentiated from Mongolian idiocy 1038  
 etiology 9 7  
 in mental deficiency 1037  
 treatment 9 8  
 Crisis Addisonian 927  
 definition 13  
 in lobar pneumonia 43  
 Croup membranous See Diphtheria 8  
 Croupous gastrocolitis 669  
 Crush syndrome 1287  
 Cryptococcosis lungs 319  
 Cryptorchidism 959  
 Current jelly sputum 147  
 Curschmann spirals in asthma 1448  
 Cushing's syndrome See Basophilism 89  
 adrenal cortex 941  
 Cutaneous leiomyoma See Omentum 1364  
 phlegmon in erysipela 1306  
 Cyanides 1466  
 Cyanosis 119 1 9 187  
 alkalosis 189  
 cardiac arrhythmias 188  
 circulatory factors in 181  
 failure 335  
 clinical conditions 18  
 edema acute pulmonary 186  
 extremities upper in thyroidea gland tumor  
 967  
 hemoglobin reduced 1 9

Cyanosis—Cont'd  
 in acute hemorrhagic pancreatic necrosis  
 774  
 laryngotracheobronchitis 137  
 massive pulmonary collapse 186 204 00  
 pleurisy with effusion 186  
 pneumothorax 186  
 in aortic dissection 188  
 in anemias 186  
 in asthma 1447  
 in bronchial asthma 183  
 obstruction 186  
 in bronchitis 183  
 in bronchopneumonia 184 185 217 18  
 2 3  
 in cardiac arrhythmias 188  
 in cervical rib 1110  
 in cholera 416  
 in chronic bronchitis 148 149  
 fibrovascular pulmonary tuberculosis  
 298  
 in circulatory disturbances of lungs 199  
 failure 335  
 in congenital cardiac lesions 181  
 heart dissection 187 4 1 42  
 in diseases of circulation 187  
 in edema of glottis 182  
 in electric shock 189  
 in emphysema 187 209 11 13  
 in foreign body of larynx 182  
 in influenza 109 111  
 in laryngeal diphtheria 85 18  
 obstruction 18  
 in laryngismus stridulus 121  
 in laryngotracheobronchitis acute 127  
 in lobar pneumonia 183 34 35 9 1  
 in mitral disease 188  
 in mustard gas poisoning 188  
 in narcotic poisoning 189  
 in new growths of bronchi 166  
 in phthisis lobar form 301  
 in pleurisy 186  
 in pneumonia 183  
 in pneumothorax 186  
 in polycythemia vera 501  
 in pulmonary atelectasis 186 201  
 atheroma 188  
 edema 186  
 emphysema 18  
 in respiratory diseases 189  
 in suffocation asphyxia 184 186  
 gas poisoning 143  
 in tracheal obstruction 189  
 in tuberculosis of lung 288  
 in tumors of bronchi 166  
 intermittent in congenital heart disease  
 18 42 4 7  
 local See Acrocyanosis 465  
 factors 18  
 massive pulmonary collapse 186 04  
 oxygen therapy in 18 185  
 persistent in congenital heart disease 428  
 physicochemical condition 188  
 rate of blood flow 181  
 respiratory factor in 180  
 Cyprus fever See Endulant fever 893  
 Cystic lesions of lungs 159 163  
 cystitis in gonorrhea 13 9  
 in typhoid fever 685  
 Cysts See also Tumors  
 bone 960  
 dermoid 160 164  
 echinococcus mediastinum 509  
 metastatic carcinoma of liver 54  
 gallbladder 767  
 in nontoxic goiter 911  
 lungs 159  
 pancreas 1  
 parasitic in diseases of liver 7 4  
 pulmonary 09  
 sarcoma 46  
 retention in disease of liver 4

## D

Dacryta syndrome 373  
 Dagestan lobar pneumonia 50  
 Danbury shakes in chronic mercury poisoning  
 1494  
 Dandy fever See Dengue 136  
 D D T in typhus fever 1254  
 Deafness 964 1004  
 from streptomycin 1425  
 in diffuse sclerosis 1087

- Death leading causes of 6  
 Death rattle 133  
 Debility 373  
 Decerebrate rigidity 991  
 Decreased contractility of blood clot in thrombocytopenia, 50  
 Deficiency diseases and stomatitis 4  
 Degenerative diseases 1135 114  
 Dehydration 46  
 in acidosis 833  
 in Addison's disease 925  
 in cholera 676  
 in diabetes mellitus 846  
 in epilepsy 1155  
 in peripheral circulatory failure 311  
 in typhoid fever 696  
 Delineation of disease See *Hypertrophic interstitial neuritis* 100  
 Delirium See *Oriental* 19384  
 Delirium in acute yellow atrophy of liver 741  
 in agranulocytosis 565  
 in lobar pneumonia 24  
 in malarial fevers 1373  
 in scarlet fever toxic type 8  
 tremors 1477 148  
 treatment 148  
 Dementia in epilepsy 1155  
 paralytic See *Paresis general* 105  
 Dengue 138 1383  
 differentiated from influenza 111  
 malarial fever 135  
 papapact fever 1383  
 relapsing fever 1360  
 smallpox 1395  
 trench fever 136  
 tautsugamu 111 ea e 1355  
 yellow fever 3  
 Dental caries 41  
 sep 41  
 Dentition 85  
 Depression mental signs in acute leptomenia 1065  
 symptomatic 10  
 Dermatitis 5  
 Dermacentor andersoni 1086  
 Dermacentroxenus richi in Rocky Mountain 1086  
 taln potted fever 157  
 Dermatitis arenic poisoning 12  
 congelation See *Frostbite* 461  
 general exfoliative 80  
 differentiated from scarlet fever 80  
 in nasuppurative mycosis 1231 13  
 orl 45  
 Dermatomyositis See *Myositis nasuppurativa* 132  
 differentiated from erythema nodosum 13  
 lupus erythematosus 141  
 rheumatic fever 13  
 scleroderma 13  
 gangrenous erythema 1466  
 Dermodycysts 160 164 99  
 Desoxycorticosterone acetate in Addison's disease 940  
 Desquamation in dengue 138  
 in measles 99 100  
 in scarlet fever 58  
 Devils group See *Pleurodynia epidemica* 1407  
 Diastolic blood pressure in congenital heart disease 42  
 Diabetes bronch See *Hemochromatosis* 384  
 in plus 385 370  
 in peripheral neuropathy 1084  
 in lipoid granulomatosis 59  
 mellitus 809  
 acid base balance 862  
 acid alkaline 847  
 carbohydrate tolerance 83  
 hypoglycemia 835  
 inulin 846  
 symptoms and signs 833  
 treatment 846  
 adrenal 814  
 albuminuria 13  
 aortic clerc 8 87 89 82  
 blood cholesterol 8  
 glucose 818  
 sugar 818 81 824  
 arterial and venous 418 571  
 curv 835  
 carbohydrate and fat metabolism 81  
 and protein metabolism 81  
 tolerance 841  
 carbun 820  
 treatment 845  
 arterial disease 82 829  
 cataract 835  
 Diabetes mellitus--Cont'd  
 cholecystitis 834  
 cholelithiasis in 834  
 clinical classification 87  
 coma treatment 846  
 complications 827  
 control of 87  
 death causes of 828  
 dehydration 46  
 diagnosis 835  
 diet 841  
 low fat high carbohydrate 841 846  
 ductless gland 814 816  
 emotional factors 1199  
 endocrine glands 813  
 epidermophytosis 821  
 etiology 811  
 exercise in 84  
 foetal value (commoner) 843 845  
 gallstones 834  
 gangrene 89 847  
 gas vascular excretion 848  
 treatment 84  
 glucose in blood 819  
 time curve 836  
 glycosuria 819 82  
 glycosuria 80  
 heredity 812  
 hunger 870  
 hypoholterolemia 8  
 hyperinsulinism 859  
 hypertension 85  
 hyperthyroidism treatment 850  
 in pregnancy treatment 856 857  
 incidence 810  
 infections treatment 81 89 849  
 insulin administration 851  
 and its action 82  
 deficiency 814  
 reaction 85  
 intercapillary glomerulonephritis 81  
 ketone bodies 82  
 lipemia 8  
 live in 816  
 nasal physiology 849  
 obesity 81  
 pancreas 3 813  
 pathological anatomy 816  
 physiology 818  
 pituitary 31  
 pneumonia in 831  
 polydipsia in 85  
 polyphagia 85  
 polyuria in 824 8  
 prognosis 828  
 protamine insulin 83  
 pruritus 828  
 psychomotoric factors 816  
 racial susceptibility 811  
 renal glycosuria 80  
 retinopathy 82  
 salivation in 46  
 sex 811  
 urgency in 87  
 symptoms and signs 824  
 in rat 835  
 thyroid 815  
 treatment 839 856  
 tuberculous in 81  
 pulmonary 819  
 urine in 821 84  
 weight loss of 876 83  
 xanthan diabetes 824  
 renal 860  
 Diabetic child 854  
 coma plus insulin depletion 833  
 polyneuritis 1095  
 retinit 59  
 Diabetes in functions to 88  
 Diabetogenic hormone 891  
 Diaphragm anatomical defects 512  
 congenital defects 13  
 diseases 51 517  
 elevation of in acute massive pulmonary  
 collapse 204  
 eventration 515  
 hernia 513  
 inflammatory lesions 17  
 intubation 51  
 paradiaphragmatic movement in emphysema 1  
 perforation 513  
 physical signs of disease 16  
 trauma crushing 513

- Cough *See* 436  
 bronchopneumonia in measles 101  
 croupy in laryngeal diphtheria 85  
 emotional factors 118  
 in acute laryngotracheobronchitis 12  
 massive pulmonary collapse 04  
 rhinitis 1  
 tracheobronchitis 12  
 in aortic aneurysm 436  
 in bronchiectasis 11 13  
 in bronchopneumonia 16 3  
 in chronic bronchitis 145  
 fibroulcerative pulmonary tuberculosis 36  
 pneumonia 9  
 in circulatory diseases 193 231  
 in diphtheria 8 11  
 in diseases of bronchi 116 13 16  
 of larynx 116 13  
 of mediastinum 09  
 of trachea 116 13  
 in emphysema 1  
 in fibrinous bronchitis 143  
 in foreign bodies of bronchi 13  
 in leukohidrosis pneumonia 3  
 in influenza 109  
 in kala azar 1358  
 in laryngotracheobronchitis acute 137  
 in lobar pneumonia 7  
 in measles 98 101 104  
 in new growths of bronchi 16  
 in pulmonary infarction 198  
 in Q fever 1361  
 in respiratory diseases 116  
 in tracheobronchitis 13  
 in tuberculosis of larynx 19  
 of lung 4  
 in ulcerative stomatitis 42  
 in whooping cough 14 1 16 1  
 paroxysmal in new growths of bronchi 165  
 symptomatic 10  
 Countertransference in mesosomatic nuclei 114  
 Cramps abdominal in achlosia 865  
 in acute mercury poisoning 1492  
 in high barometric pressure 1458  
 heat 1456  
 muscle in cholera 876  
 Cranial nerves 986 1006  
 operation in serous meningitis 207  
 trauma in serous meningitis 107  
 Craniopharyngioma intracranial tumors 119  
 pituitary gland 904 90  
 tumors symptoms and signs 904  
 Craniotomy in chronic adhesive arachnoiditis 108  
 Cranium biddum 1036  
 Crepitations in trachea and bronchi diseases 133  
 Cretinism 97 929  
 differentiated from Mongolian idiosyncrasy 1038  
 etiology 97  
 in mental deficiency 1037  
 treatment 98  
 Cri in Addisonian 927  
 definition 13  
 in lobar pneumonia 243  
 Croup membranous *See* Diphtheria 82  
 Croupous gastrocolitis 669  
 Crush syndrome 1287  
 Cryptococcosis lungs 319  
 Cryptorchidism 959  
 Current jelly putum 167  
 Cushing's spirals in asthma 1448  
 Cushing's syndrome *See* Basophilism 89  
 adrenal cortex 311  
 Cutaneous leishmaniasis *See* Oriental sore 1284  
 phlegmon in erysipelas 1306  
 Cyanides 1486  
 Cyanosis 119 19 121  
 alkalosis 189  
 cardiac arrhythmias 188  
 circulatory factors in 181  
 failure 385  
 clinical conditions 18  
 edema, acute pulmonary 186  
 extremities upper in thymus gland tumor 967  
 hemoglobin reduced 179  
 Cyanosis—Cont'd  
 in acute hemorrhagic pancreatic necrosis 774  
 laryngotracheobronchitis 137  
 massive pulmonary collapse 186 04 05  
 pleurisy with effusion 186  
 pneumothorax 186  
 in aortic diseases 186  
 in apiculate 186  
 in asthma 1467  
 in bronchial asthma 183  
 obstruction 186  
 in bronchitis 183  
 in bronchopneumonia 164 18 17 18  
 in cardiac arrhythmias 188  
 in cervical rib 1110  
 in cholera 66  
 in chronic bronchitis 148 149  
 fibroulcerative pulmonary tuberculosis 798  
 in circulatory disturbances of lungs 197  
 failure 33  
 in congenital cardiac lesions 181  
 heart disease 18 121 4  
 in diseases of circulation 181  
 in edema of lottis 187  
 in electric shock 165  
 in epistaxis 18 22 23  
 in foreign body of larynx 149  
 in influenza 100 121  
 in laryngeal diphtheria 85 18  
 obstruction 18  
 in laryngismus stridulus 121  
 in laryngotracheobronchitis acute 12  
 in lobar pneumonia 183 34 35 2 1  
 in mitral diseases 183  
 in mustard gas poisoning 133  
 in narcotic poisoning 189  
 in new growths of bronchi 166  
 in phthisis lobar form 391  
 in pleurisy 186  
 in pneumonia 143  
 in pneumothorax 186  
 in polycythemia vera 551  
 in pulmonary atelectasis 186 01  
 atheroma 188  
 edema 186  
 emphysema 18  
 in respiratory diseases 18  
 in subcutaneous cataract 164 166  
 gas poisoning 143  
 in tracheal obstruction 187  
 in tuberculosis of lung 88  
 in tumors of bronchi 166  
 intermittent in congenital heart disease 18 427  
 local *See* Acrocyanosis 46  
 factors 187  
 massive pulmonary collapse 186 04  
 oxygen therapy in 182 183  
 persistent in congenital heart disease 426  
 physico-chemical conditions 183  
 rate of blood flow 181  
 respiratory factor in 180  
 Cyanus fever *See* Indurant fever 693  
 Cystic lesions of lungs 159 163  
 Cystitis in gonorrhea 1329  
 in typhoid fever 685  
 Cysts *See* also Tumors  
 bone 966  
 dermoid 160 164  
 echinococcus mediastinum 509  
 metastatic carcinoma of liver 54  
 gallbladder 67  
 in nontoxic goiter 911  
 lungs 169  
 pancreas 5  
 parasitic in diseases of liver 54  
 pulmonary 69  
 ramula 40  
 retention in disease of liver 4  
 D  
 Da Costa syndrome 33  
 Dagnan lobar pneumonia 250  
 Danbury shake a chronic mercury poisoning 1491  
 ing 1491  
 Danby fever *See* Deigue 118  
 D D T in typhus fever 1354  
 Deafness 964 1004  
 of streptomycin 1425  
 in diffuse sclerosis 1087



## Dysporica, 1364

- Diarrhea 647 See also *Dysentery amebic*  
 60 *Dysentery bacillary* 63  
 and *Enterocolitis acute catarrhal*  
 668  
 xerosis in 86  
 emotional factors 119  
 hemorrhagic See *Melena*  
 in acute infectious hepatitis 3  
 in Addison's disease 535  
 in amebic dysentery 640  
 in bacillary dysentery 673  
 in cholera 67  
 in diphtheria, 84  
 in diseases of large intestines 647  
 in food infections 1497  
 in foot and mouth disease 1344  
 in parasitic stomatitis 34  
 in pellagra 79  
 in regional ileitis 678  
 in relapsing fever 1360  
 in scarlet fever toxic type 8  
 in scurvy 91  
 in exum disease 1438  
 in simple stomatitis 34  
 in Swineherd's disease 136  
 in typhoid fever 659  
 intermittent 1  
 ileenteric 668  
 of ricket differentiated from celiac disease 644  
 symptomatic 9  
 Diarrhea in leprosy 1409  
 Diathesis hemorrhagic in congenital syphilis 131  
 Diazo reaction in typhoid fever 681  
 Dichloro dihydroxy trichloro ethane in typhus fever 134  
 Dick test 80 81  
 Diet detergent, dental caries 41  
 Diet's crises 1 36  
 Di trich's plugs bronchiectasis 1 11  
 Diffuse myelitis with optic neuritis See  
*Neuromyelitis optica* 114  
 symmetrical lipomatose 383  
 Digestion physiology of 6 9 620  
 Digitalis in heart disease 363 36 394  
 poisoning 363 395  
 Dihydroxy ethin treatment in atrophic rhinitis 3  
 Dilantin in epilepsy 1157  
 Dimercipol in chemical intoxications 40  
 Diphtheria 8 94  
 age in 82  
 anatoxin 91  
 antitoxin 90 9  
 auriculoventricular block 3  
 Bacillus diphtheriae 8 84 89  
 brachycardia (forti fits) 8  
 carriers 83 89  
 causative agent 8  
 circulatory failure 93  
 convalescence 93  
 course and termination 37  
 cyanosis in 85  
 diagnosis of 88  
 differential diagnosis 88 10  
 differentiated from acute follicular tonsillitis 51 88  
 measles 102  
 scarlet fever 3 9  
 ulcerative stomatitis 41  
 Vincent's angina 88  
 whooping cough 1 8  
 dyspnea in 8 8 93  
 heart extrasystoles 85  
 failure 86 88  
 in parenchymatous degeneration of myocardium 406  
 in scarlet fever 9  
 individual protection 90  
 susceptibility 89  
 infections multiple legion 86  
 inoculation period 83  
 iron lung in 93  
 laryngeal 87  
 cyanosis in 18  
 differentiated from laryngotracheobronchitis 137  
 intubation 92  
 laryngitis 38  
 symptoms 8  
 tracheotomy in 9

## Diphtheria—C. and

- larynx in 83  
 mediastinal emphysema acute 10  
 mortality in 91  
 nares in 83  
 nasal mucous membrane in 8  
 nervous system in 87  
 orally in 8 93  
 pathological anatomy 83  
 peripheral neuritis in 8  
 pharynx in 83 8  
 predisposing factor 83  
 protection of the individual 90  
 Schick test 3 80 88 89 90  
 secondary lesions 86  
 sinoauricular block 8  
 sore throat in 84  
 symptoms 84  
 syncope 8  
 toxemia 84  
 toxin antitoxin protection 90  
 tracheotomy in 9  
 treatment 91  
 tricuspid valvular insufficiency 8  
 vasomotor collapse 8 88  
 vulva in 83  
 wound infection 86  
 Diphtheritic neuritis 109  
 Diphterobothria (a symptom) 84  
 Diplopia cerebral infantile 1040  
 Diplopia in epileptic encephalitis 108  
 Diplopia 1460  
 Diplopia 14 87  
 Discharge yellow in gonorrhea 1330  
 Diseases caused by blood sucking in ectoparasites 1366 1384  
 lice fleas ticks and other biting in ectoparasites 1349 1366  
 Dissection of 16  
 histological factors 10  
 of unknown origin 1136  
 prognosis of 1  
 treatment of 17  
 Disminuted myelitis with optic neuritis See  
*Neuromyelitis optica* 114  
 sclerosis See Multiple sclerosis 1140  
 Distomatia pulmonary differentiated from acute spirochetal bronchitis 14  
 Diuretic in acidosis 86  
 Diuretics in cardiac failure 367  
 Diversa pulvis See *Barometrie pressure effects of* 1457  
 Diverticula 8 9 See also *Foecopyrus diseases of diverticula* 588  
 celiac 661  
 cephagus traction 593  
 celiac 604  
 Meckel 660  
 pulsation cephagus 93  
 small intestine 653  
 Diverticulitis 661  
 treatment 66  
 Diverticulosis 661  
 Dizziness in intracranial trauma 1104  
 distomatia 10  
 Dropsical at 395  
 Drug rash differentiated from scarlet fever 40  
 Drug disease due to 14 6  
 Dry mouth alveolar gland 46  
 tongue alveolar gland 46  
 Ductless glands of 888 See also  
 Endocrine diseases 8  
 Adrenocortical function 936  
 anterior 95  
 carotid body 963 91  
 Diabetes mellitus 814 816  
 gonads abnormal malfunctions of 959  
 Hypogonadism 946 91  
 Hypogonadism 346 903  
 hypotension 91  
 introfuction 888  
 male climacteric 9 0  
 menorrhagia 9 7  
 menstruation 9 4  
 di turban 9 3  
 puberty 945  
 fertility 9 0 959  
 Ductal arteriosus present in congenital heart disease 4  
 Duodenal taenia 634 635  
 ulcer 60  
 Duodenitis 631





## 1 lema—Cont 1

- liver circulation 17
- lungs 118 130 134
  - in asthma 1448 1449
  - in bronchopneumonia 16
  - in essential hypertension 449
  - in influenza 110
- nutritional 83
  - diet deficiency 784
  - differentiated from beriberi 88
  - in acute wet beriberi 8
- pulmonary 186
  - cyanosis in 186
  - in lobar pneumonia 41
  - calc in lateral sinus thrombosis 1116
  - treatment 1 79
- Effort syndrome 3 3
  - mustard gas poisoning 139
- Effusion erythrinous pericarditis in acute
  - rheumatic fever 61
  - erous in new growths of bronchi 169
- Ehrlich diazo-reaction 4
  - urine in measles 10\*
- Eisenmenger's complex 4 3
- Electric shock, eff. cts 1473 1474
  - cyanosis 189
- Electrocardiogram 334 404
  - in acute rheumatic fever 38 39
  - in coronary arteries of cases 4 4 1 6
  - normal 343
- Electrocution 35 14 3
- Electroencephalography in epilepsy 1104
- Elephantiasis 13 8 138
  - differentiated from deformities in neurofibromatosis 1136
- Emaelation progressive in Simmonds disease 339
- Emboli in coronary arteries 31 4 4 6
- Embolism brain vascular lesions, nervous
  - system 111 1113
  - pulmonary in chronic pneumonia 6
  - infarction 194
- Emmenia in migraine 11 8
- Emotional conflicts See Psychosomatic medicine 1161 120
  - disturbances and organ function 116
  - factors in hypertension 118
  - in tabidity menopause 9 6
  - phere psychosomatic disorder 1169
- Emphysema 05 14 3 0
  - acute interstitial 06
  - mediastinal 510
  - vesicular 06
  - causative agents 06
  - circulation disturbance 11
  - compensatory 0
  - cough in 10
  - cour and termination 12
  - cyanosis in 187 09 11 13
  - diagnosis 13
  - dyspnea in 09 11
  - heart in 11 14
  - hypertrophic 207
  - in bronchiectasis 1 3
  - in chronic bronchitis 148
  - in multiple myeloma 120
  - in pulmonary tuberculosis 303
  - in whooping cough 1
  - of lung 160 18
  - pathological anatomy 08
  - pulmonary circulation changes 08
  - cyanosis in 18
  - senile 06
  - signs 1
  - subcutaneous esophagus 588
  - symptoms 209
  - synonyms 0
  - thoracic wall change 08
  - treatment 13
  - type 05
- Empyema chronic of gallbladder 61
  - differentiated from lobar pneumonia 43
  - 48
  - gallbladder 61
  - in bronchiectasis 156
  - in measles 101 103
  - in pleurisy 490
  - parulert 491
  - necrotic in lobar pneumonia 19 48
  - of accessory sinuses in rhinitis acute 1
  - tuberculous 494
- Encephalitis 1081 1082
  - acute associated with acute lymphocytic meningitis 10 8

## Encephalitis acute—Cont d

- in measles 10
- pathological anatomy 1084
- differentiated from botulism 1498
- diffusa periaxialis 108
- epidemic, 1081 1084
- in paralysis agitans 108 1083 1117 1118
- sequelae differentiated from chorea, 61
- equine 1086
- in chickenpox 1400
- in influenza 111
- in mumps 96
- in smallpox 1398
- in tsutsugamushi disease 13 0
- lethargica, 1081
- in dystonia musculorum deformans 114
- torticollis 1148
- St Louis type 1082
- tuberculous, in tuberculous meningitis 10 4
- type 1 See Encephalitis epidemic 1081
- Encephalography 1031 103
- in epilepsy 1154
- in intracranial trauma, 1104 1105
- Encephalomyelitis 1088
  - acute its etiology, 1084
- Encephalopathy lead, 1040 1489
- Enchondromatosis, multiple See Enchondroses, multiple congenital 1 14
- Enchondroses, multiple congenital 1 14 1 15
- Endarteritis obliterans See Thromboangiitis obliterans 466 46
- Endemic typhus 135
- Endocardial lesion acute follicular ton illiti 51
- Endocarditis bacterial 409
  - acute bacteriology 414
  - diagnosis 418
  - differentiated from malarial fever 13
  - gonococcal 413
  - influenzal 41
  - pathological anatomy 416
  - pneumococcal 41
  - prognosis 420
  - rheumatic fever 409 419
  - taphylococcal 414
  - streptococcal hemolyticus in locarditis 41
  - sypthills 408
  - subacute 409
  - anemia in 409
  - differentiated from idiopathic hypochromic anemia, 34
  - lupus erythematosus disseminatus 1413
  - malaria 13
  - café-au-lait pigmentation 411
  - clubbing of fingers 410 411
  - differentiated from undulant fever 690
  - emboli 410
  - glomerulonephritis 411
  - hematuria in 411
  - hemorrhages, apintier like 411
  - Iliac nodes 411
  - pericarditis 410
  - petechiae 410
  - pigmentation 411
  - Streptococcus viridan 409
  - symptoms and signs, 410
  - treatment, 4 0
  - differentiated from typhoid fever 638
  - gonorrheal ophthalmic lesions 1334
  - in epidemic follicular tonsillitis 3
  - in influenza 111
  - in mumps 96
  - in rheumatic fever acute 9 60 61
  - in scarlet fever 6
  - influenzal 41
  - lenta. See Endocarditis bacterial subacute 409
  - malignant in scarlet fever 6
  - pneumococcal 41
  - staphylococcal 414
  - streptococcal hemolyticus 41
  - Endocarditis lesions 408 4 1
  - Endocrine deficiency symptomatic 16
  - gland dysfunction in hereditary progesterone muscular dystrophies 10 0
  - glands in carbohydrate metabolism 813
  - diseases of 688
  - nervous system relationship 98 10 2
  - system and metabolism in psychosomatic medicine 1198
  - emotional factors 1198

- Foreign bodies bronchi factor in—Cont'd  
 bronchitis chronic, 148  
 chronic pneumonia 59 0  
 infection of lung 1 3  
 symptoms 173  
 treatment, 1 5  
 in gastrointestinal tract, 663  
 in larynx cyanosis in 18  
 Forest jaws See *Espundia* 1386  
 Fractures spontaneous in celiac disease 641  
 in osteopetrosis 1 18  
 Fragilis o sificans See *Osteogenesis hyper*  
*fecta* 1 15  
 Fragilitas ossium See *Osteogenesis impropria*  
*fecta* 1 15  
 Frambesia. See *Leish* 13 4  
 Frequency of urination asymptomatic 10  
 Friedlander pneumonia 3  
 pain in 3  
 sputum in 23  
 Friedlander's bacillus 145 150 3  
 causative agent of chronic bronchitis 14  
 in bronchiectasis 150  
 Friedreich's ataxia 104  
 differentiated from ataxia cerebellar hereditary 1043  
 differentiated from chorea 5  
 Erblich's syndrome 883 897 899  
 diagnosis symptoms treatment 898 899  
 differentiated from obesity in diseases of gonads 8 3  
 in endogenous obesity 880  
 obesity 883  
 Frohn's syndrome 1081 1125  
 in extradural abscess of the cord 1081  
 Frontier sore See *Oriental sore* 1384  
 Frostbite 461 46  
 differentiated from Raynaud's disease 4 5  
 Frothing at mouth in epilepsy 11 1  
 Fullness symptomatic 5  
 functional histosteronias See *Esophagus*  
*dyphagia functional* 592  
 Fungus infectio n n o c 3  
 Fusospirillosis See *Stomatitis ulcerata* 14 4

## G

- Gaffky scale in tuberculosis of lungs 81  
 Gait disturbance of in carbon monoxide poisoning 1465  
 Gaiterpain fever See *French fever* 1335  
 Galactose 1 1 in carbohydrate metabolism 22  
 Gallbladder diseases of 59 62 834  
 acute inflammations 59  
 anomalies 758  
 biliary drainage 7 7  
 obstruction 58  
 carcinoma of 788  
 cholecystitis gangrenous 60  
 cholecystography 8  
 empyema 61  
 function, 7 5  
 inflammations 759  
 methods of examination 58  
 sarcoma of 88  
 tumors 67  
 Gallstones See *Cholelithiasis* 62  
 in diabetes mellitus 834  
 Ganglioneuromas 1127  
 carotid gland 871  
 suprarenal medulla, 943  
 Gangrene cause of 829  
 in appendicitis 6 6  
 in bronchiectasis 156  
 in diabetes mellitus 8 9 847  
 in ergot poisoning 1496  
 in gangrenous erythema 1496  
 in thromboangitis obliterans 467  
 lung 255  
 in bronchiectasis 1 6  
 in bronchopneumonia 0  
 in lobar pneumonia, 247  
 nondiabetic 829  
 Gangrenous erythema 1496  
 dermatomyositis 1496  
 erythromelalgia 1496  
 Raynaud's disease 1496  
 scleroderma 1496  
 thromboangitis obliterans 1496  
 tomatitis 45

- Gantz test in benzene poisoning 1468  
 Gas poisoning cause of chronic bronchitis 147  
 respiratory system 137 138  
 poisons 1448  
 Gasoline poisoning 1496  
 Gastric See also *Stomach* 598  
 acidity determination 604 605  
 analysis in carcinoma 621  
 atony 6 8  
 digestion pepsin 606  
 mucus, 606  
 neuroses 6 6 1191  
 secretion 602 603  
 tetany 954  
 ulcer 607 See also *epileptic ulcer*  
 aluminum hydroxide therapy 614  
 carcinomatous changes 611  
 complications 610  
 diagnosis 61  
 differentiated from carcinoma of stomach 612  
 differentiated from syphilis of stomach 618  
 etiology 607  
 gastric analysis 609  
 hemorrhages 610  
 magnesium trisilicate therapy 614  
 occult blood 610  
 pain 608  
 pathological lesions 611  
 perforation 610  
 prognosis 61  
 pyloric obstruction, 611  
 symptoms 607  
 treatment 612  
 vomiting in 609  
 x ray in 611 61  
 Gastritis acute 6  
 chronic 6 4  
 achlorhydria in 6  
 diagnosis 614  
 etiology 6 4  
 gastrocopes in 6 5  
 treatment 628  
 suppurative 623  
 Gastrocolitis croupous 469  
 Gastroenteritis differentiated from epiglottitis 1070  
 in Friedlander's pneumonia 23  
 Gastrointestinal allergy 14 0  
 symptoms in acute anterior poliomyelitis 1090  
 in Addison's disease 935  
 in pellagra 79  
 system emotional factors 1189  
 psychosomatic medicine 1189  
 tract emotional factors 1189 1194  
 foreign bodies 663  
 hemorrhage differentiated from chronic hepatitis 11  
 symptomatic, 9  
 tularemia 1336  
 Gastrojejuno colic fistula 533  
 Gastroscope in diagnosis of gastrointestinal pathology 606  
 Gaucher's disease See also *Splenomegaly*  
 in gel 576  
 differentiated from lipid histiocytes 5 8  
 differentiated from plenic anemia 553  
 Gec's disease See *Celiac disease* 541  
 Gee Herter's disease 610 641  
 G e Thayer's disease 641  
 Gelineau's disease See *Varicella* 1156  
 Genital phage psychological development 1166  
 Genitourinary symptoms symptomatic 10  
 system See also *Urinary system diseases*  
 of 1 15  
 Geographical tongue 38  
 Geophagia in gastric neuroses 627  
 Geotricho'sia in lungs 321  
 German measles See *Rubella* 104  
 Giardiasis *Giardia lamblia* 11  
 Gibraltar fever See *Undulant fever* 893  
 Gigantism 892  
 pituitary tumor 892  
 sexual immaturity 892  
 x ray in 891 892  
 Gicht in disease differentiated from cryptococcosis of lung 319  
 Ginger paralysis 1481

## 1. Pathology diseases of—Cont'd

- functional 590
- inflammations 588
- pain 586
- paralysis 91
- peptic ulcer 589
- pharynx incoordination of muscles 591
- paralysis of muscles 590
- regurgitation 586 590
- stenosis 586 590
- strangling or choking 586
- subcutaneous emphysema 588
- symptomatology 86
- traumatic lesion 88
- tumors benign 595
- malignant 596
- symptoms 598
- ulcer 589
- l. spundia 1386
- l. stat fetal See *Lung atelectasis* 199
- l. stat marbré of Oppenheim and Vogt See *Athetosis* double 1041
- l. thyl alcohol 14.6 1480
- l. typhosa in typhoid fever 680
- European blastomycosis 319
- relapsing fever See *Relapsing fever* 1359
- Exanthemata differentiated from epidemic cerebro spinal meningitis 10.0
- Exhaustion syndrome 933
- Exophthalmic goiter See *Goiter exophthalmic* 914
- Exophthalmos in acrocephaly 1 8
- in cavernous sinus thrombosis 1116
- in exophthalmic goiter 914 915
- in general hyperkeratosis of skull 1
- in lipid granulomatosis 5 9
- Exostoses multiple cartilaginous 1 13
- Expectoration character of 116
- in acute tracheobronchitis 135
- in bronchi disease of 132
- in bronchiectasis 151 1
- in bronchitis fibrinous 143
- in diseases of trachea and bronchi 13
- symptomatic 10
- Expressive psychotherapy 11 5
- Extradural abscess of cord cord compression signs 1081
- Extrapyramidal disease See *Various systems extrapyramidal pathways* 991
- Extravasates diptheria 85
- Exudate signs in parenchyma of lungs 190
- Exudative tonsillitis of unknown cause 3
- Diagnosis in riboflavin deficiency 759
- lesions of lewisite cause of 14
- treatment of in measles 101 103

## F

- Facial expression in cretinism 9 8
- in myxedema 9 4
- paralysis 1003
- in rumps 96
- Facies flushed in typhus fever 13 2
- in epidemic encephalitis 108
- masklike appearance in leprosy 140.
- plethoric in basophilism 89
- Maintaining symptomatic 10
- Falx cerebri 981
- Ferrillal purpura 5 3
- Family periodic paralysis 1043
- treatment 1044
- Famine fever See *Relapsing fever* 1359
- Farcy See *Glanders* 1359
- Fatigability in cardiac failure 3 4
- in myasthenia gravis 1143
- symptomatic 8
- Fatigue in diptheria 84
- in suffocative gases 143
- Febrius recurrens See *Relapsing fever* 1359
- Fecundity See *Mental deficiency* 1037
- Fifty syndrome in rheumatoid arthritis 124
- Female gonads abnormality 951
- Fern (male) extract intoxication 739
- Festination paralysis agitans 1117
- Festination paralysis agitans 1117
- Fever See also *Pyrexia*
- in acute follicular tonsillitis 51
- glossitis 37
- rheumatic fever 57
- in bronchopneumonia 20
- in carbuncle of upper lip 37
- in chorea 62

## Fever—Cont'd

- in chronic hepatitis 14
- in dermatomyositis 1 3
- in endophthalmitis St Louis type 108.
- in epidemic follicular tonsillitis 5
- in foreign bodies of bronchi infections 17
- in herpes zoster 1401
- in influenza 109
- in leucemia 555
- in lobar pneumonia 231
- in lymphocytic choroid meningitis 1401
- in measles 98
- in mumps 95
- in new growths of bronchi 168
- in paralysis acut flaccid 1089
- in pernicious anemia 529
- in regional ileitis 6 8
- in retropharyngeal abscess 9
- in scarlet fever 7
- in stomatitis simple 34
- in tsutsugamushi disease 1354
- in tuberculosis of lung 783 286 9
- in typhoid fever 650
- in undulant fever 593
- in use of sulfonamides 1218
- in whooping cough 1 6
- relapsing 1359
- symptomatic 9
- Fibrillary twitchings in progressive muscular atrophy 1146
- Fibrinous bronchitis See *Bronchitis fibrinous* 143
- Fibrosarcoma meningeal 1127
- perineural 1128
- Fibroid nodules in acute rheumatic fever 64
- in rheumatoid arthritis 1243
- tuberculous See *Tuberculosis fibroid* 301
- Fibroma nasopharyngeal 6 30 3
- of larynx 131
- Fibrosis chronic pulmonary 359
- bronchiectasis 153
- in lung 148 190
- interstitial caused by mustard gas poisoning 139
- signs in parenchyma of lungs 190
- Fibrositis definition 1230
- Fibrous dysplasia 1 19
- Filarial lymphangitis 13 9
- Filaria 13.8 1379
- ekphrastic due to 13 8
- eosinophilic granulocytes 527
- Filaria bancrofti 1378
- parasites causing 13 8
- Filtrable virus See *Virus filtrable* 11 36
- 1345 1383 1400
- Finger drop in peripheral nerve trauma 1108
- Fire damp 1460
- Fissures mouth in congenital syphilis 1317
- Fistula gastro jejuno colic 633
- Fits uncinata 1008 1009
- in temporal lobe tumors 1131
- Five day fever See *Trench fever* 13 5
- Fixation 1177
- Flutulence 601
- symptomatic 9
- Fleck typhus See *Typhus fever* 1351
- Fleckfeber See *Typhus fever* 1351
- Flocculation tests in liver function 9
- Flu See *Influenza* 106
- Fluctuation wave peritonitis 503
- Fluke infections See *Trematode infections* 710
- Focal spread symptomatic 13
- follicular tonsillitis penicillin in 5
- sulfathiazole and sulfadiazine 11
- Food deficiency symptomatic 16
- infection 1497
- intoxication 1498 1499
- values (commoner) table 843 845
- Foot and mouth disease 1344
- Foot drop in lead neuritis 1095
- in paralysis of peroneal nerve 1109
- in peripheral neuritis 1480
- Foreign bodies in bronchi 1.2 1 6
- bronchial obstruction 172 175
- cause of infection 17
- diagnosis 175
- differentiated from acute massive pulmonary collapse 64
- differentiated from pulmonary tumors 171
- factor in bronchiectasis 150 153 154
- 1 3

foreign body's bronchi factor in—Cont 1  
 bronchitis chronic, 148  
 chronic pneumonia 9  
 infection of lung 13  
 symptoms 13  
 treatment, 17  
 in gastrointestinal tract 663  
 in larynx cyanosis in 18  
 forest jaws See *Espana* 1356  
 fractures spontaneous, in cell disease 41  
 in osteopetrosis, 118  
*Fragilis ossificans*. See *Osteogenesis imperfecta* 115  
*Fragilitas ossium*. See *Osteogenesis imperfecta* 111  
*Frambesia*. See *Laws* 1324  
 frequency of urination symptomatic 10  
 Friedländer pneumonia 3  
 pain in 23  
 sputum in 3  
 Friedländer's bacillus 143 150 3  
 causative agent of chronic bronchi in 14  
 in bronchiectasis 10  
 Friedreich's ataxia, 104  
 differentiated from ataxia, cerebellar hereditary 1043  
 differentiated from chorea 6  
 Fröhlich's syndrome 333 339 339  
 diagnosis symptoms treatment 333 339  
 differentiated from obesity in diseases of gonads 33  
 in endogenous obesity 330  
 obesity 333  
 Froin's syndrome 1031 113  
 in extradural abscess of the cord 1031  
 Front's sore See *Oriental sore* 1334  
 Frothing 481 45  
 differentiated from Raynaud's disease 45  
 Frothing at mouth in epilepsy 111  
 Fullness symptomatic 8  
 Functional hyaline tenosis. See *Esophagus dysphagia functional* 55  
 Fungus infections in 3  
 Pseudo-pyralis See *Stomatitis ulcerative* 4

G

Gaffky scale in tuberculosis of lungs 91  
 Galt, disturbance of in carbon monoxide poisoning 146  
 Gatterpain fever See *French fever* 135  
 Galactose test in carbohydrate metabolism

Gallbladder diseases of 739 834  
 acute inflammations 9  
 anomalies 55  
 biliary drainage  
 obstruction 8  
 carcinoma of 83  
 cholecystitis gangrenous 60  
 cholecystography  
 empyema, 81  
 function, 5  
 inflammation 59  
 methods of examination 55  
 sarcoma of 83  
 tumors 83  
 Gallstones See *Cholelithiasis* 6  
 in diabetes mellitus 834  
 Gangliocarcinoma 117  
 carotid gland 971  
 suprarenal medulla, 943  
 Gangrene cause of 323  
 in appendicitis 656  
 in bronchiectasis 16  
 in diabetes mellitus 829 847  
 in ergot poisoning 1496  
 in gangrenous ergotism 1496  
 in thromboangiitis obliterans 46  
 lung 255  
 in bronchiectasis 156  
 in bronchopneumonia 0  
 in lobar pneumonia, 247  
 nondiabetic, 83  
 Gangrenous ergotism 1496  
 dermatomyositis 1496  
 erythromelalgia, 1496  
 Raynaud's disease 1496  
 scleroderma 1496  
 thromboangiitis obliterans 1496  
 stomatitis 45

Gant's test in benzene poisoning 1468  
 Gas poisoning cause of chronic bronchitis 147  
 respiratory system 12 138  
 poisons 1468  
 Gasoline poisoning 149  
 Gastric. See also *Stomach* 593  
 acidity determination, 604 605  
 analysis, in carcinoma, 621  
 atony 68  
 digestion pepsin, 606  
 mucus, 106  
 neuroses 66 1191  
 secretion, 603 60  
 tetany 366  
 ulcer 607 See also *Peptic ulcer*  
 aluminum hydroxide therapy 614  
 carcinomatous changes 611  
 complications 410  
 diagnosis 41  
 differentiated from carcinoma of stomach, 41  
 differentiated from syphilis of stomach 616  
 etiology 607  
 gastric analysis 609  
 hemorrhages 610  
 magnesium trisilicate therapy 614  
 occult blood 610  
 pain, 608  
 pathological lesions 411  
 perforation, 610  
 prognosis, 612  
 pyloric obstruction, 411  
 symptoms 607  
 treatment, 613  
 vomiting in, 609  
 x ray in, 611 61  
 Gastritis acute, 6  
 chronic, 6  
 achlorhydria in 6  
 diagnosis, 6  
 etiology 6  
 gastroscopes in 6  
 treatment, 626  
 suppurative 43  
 Gastrocolitis croupous 665  
 Gastroenteritis differentiated from epileptic cerebro-pal meningitis 100  
 in Friedländer's pneumonia 3  
 Gastrointestinal allergy 1450  
 symptoms in acute anterior poliomyelitis 1030  
 in Addison's disease 930  
 in pellagra, 93  
 system emotional factors 1189  
 psychosomatic medicine 1189  
 tract, emotional factors 1189 1194  
 foreign bodies 663  
 hemorrhage differentiated from chronic hepatitis 743  
 symptomatic 8  
 tularemia, 1334  
 Gastro-jejuno-colic fistula, 623  
 Gastroscopy in diagnosis of gastrointestinal pathology 606  
 Gaucher's disease See also *Splenomegaly*  
 large celled 54  
 differentiated from lipid histiocytosis 58  
 differentiated from splenic anemia 53  
 Gee's disease. See *Celiac disease* 642  
 Gee Herter's disease 640 641  
 Gee-Thayssen's disease 641  
 Gelineau's disease See *Narcolepsy* 1158  
 Genital phenomena psychological development, 1166  
 Genitourinary symptoms symptomatic 10  
 system. See also *Urinary system diseases* of 150  
 Geographical tongue 38  
 Geopagia in gastric neuroses 68  
 Geotrichosis in lungs 31  
 German measles. See *Rubella* 104  
 Gardiasis See *Ardis lambia* 11  
 Gibraltar fever See *Undulant fever* 633  
 Gigantism 89  
 pituitary tumor 392  
 sexual immaturity 392  
 x ray in 391 89  
 Gilchrist disease differentiated from cryptococcosis of lungs, 319  
 Ginger paralysis 1481

- Glands 1330 1341  
nose infection 73  
swelling saladenitis 41  
Glands cervical enlargement in myxoma  
    anx tumors 6  
ductless See *Ductless glands* 888  
enlarged in new growth of bronchi 140  
lymphatic See also *Lymph glands dis-*  
    eases of 581  
    enlargement in tonsillitis 51  
    salivary See *Salivary glands* 46  
    swelling See *Swelling glands*  
Glandular fever 8 See also *Mononucleosis*  
    acute 140  
    differentiated from mumps 97  
    lasspock See *Chickenpox* 1399  
Glioblastoma multiforme 11  
Gliomas 112  
Globulin extracts in measles 103  
Globus hystericus 1190  
Glomerulonephritis acute 16  
    in scarlet fever 9  
    chronic 166 1969  
    Cheyne-Stokes syndrome 1 1  
    visual disturbances 1 111  
    differentiated from nephrosis 1 4  
    hematuria in 1 65  
    in subacute bacterial endocarditis 411  
    streptococcus infection 1 83  
Glomeruloclerosis intercapillary 1 4  
Glossitis in trypanosomiasis 1389  
Glossitis See also *Tongue diseases of* 3  
    acute 3  
    penicillin in 37  
    chronic 38  
    in idiopathic tenosynovitis 642  
    in subacute hepatitis 144  
    Moeller's 38  
Glossopharyngeal neuralgia, 1149  
Glottis edema of 13  
    cyanic 18  
Glucose threshold in diabetes 819  
    time curve in diabetes 836  
Glycosuria in diabetes mellitus 819 83,  
    in exophthalmic goiter 918  
    in hyperglycemia 89  
    renal See *Renal glycosuria* 860  
    in pregnancy 860  
Goat fever See *Undulant fever* 693  
Goiter 908  
    adolescent 909  
    basal metabolic rate 910  
    etiology 910  
    colloid 908  
    exophthalmic 914  
    blood chemistry 916  
    diabetes mellitus 918  
    diet in 918  
    differentiated from pulmonary tubercu-  
    losis 917  
    exophthalmos 914 91  
    heart symptom 91  
    hyperthyroidism 91  
    iodine in 916 918 940  
    metabolism in 916 917  
    Moebius sign 916  
    myocardial disease in 91  
    nervous symptoms 914 916  
    pathology 916  
    rest treatment 918  
    Steinwald sign 916  
    thyroidectomy 918 921  
    treatment 918 91  
    von Graefe's sign 916  
    x-ray treatment 921  
    in laryngeal paralysis 12  
    intrathoracic differentiated from new  
    growth of bronchi 140  
    pulmonary tuberculosis 11  
    nontoxic 911  
    symptoms and sign 910 91  
    thiouracil in 11  
    toxic 913  
Gold therapy in rheumatoid arthritis 148  
Gonadotropic factor of pituitary prepara-  
    tions 899  
    function in acromegaly 895  
    hormone, 891  
Gonads Developmental abnormality 946  
    951 959  
    diseases of 944 960  
    dysfunction 953  
    pituitary hormones in 899  
Gonads—Cont 1  
    hyperfunction 946  
    hypergonadal function 946  
    hypofunction 947  
    treatment 953  
    introduction 944  
    menopause 96  
    estrogenic substances in 96  
    psychomotoric medicine 140  
Gonococcal endocarditis 413  
Gonococcus in gonorrhea 1329  
    in septic arthritis 136  
    in septicemia 1302  
Gonorrhea 139 1344  
    arthritis 1330 1333  
    conjunctivitis 131  
    diet in 1334  
    differentiated from lymphopathia vene-  
    reum 138  
    differentiated from syphilis 1308  
    endocarditis 413 133 1334  
    epithelial lesion 134  
    etiology 139  
    female 139  
    fixation test 1337  
    hyperkeratosis 1331  
    tri-oculitis in 1331  
    local lesions 132  
    male 139  
    ophthalmia 1334  
    pathological anatomy 1332  
    penicillin in 1334 1432  
    primary lesions 1332  
    prophylaxis 1333 143  
    rectal stenosis 133  
    skin lesions 1331  
    sterility in 1330  
    stomatitis 135  
    sulfonamides in 1334 1437  
    symptoms and signs 139  
    synonym 1329  
    systemic infection 1330  
    treatment, 1333  
    urethritis in 139  
Gout 80 87  
    acute 871  
    alcohol 871  
    blood examination 8  
    bony changes 81 82  
    chronic 873  
    complication 876  
    diagnosis 874  
    diet in 876  
    differentiated from benign lymphogranu-  
    loma 317  
    rheumatoid arthritis 80 144 1246  
    drugs in 8  
    excess protein consumption 871  
    heredity 871  
    kidneys in 876  
    lead poisoning and 871 1489  
    prophylactic 87  
    test diets 86  
    tophi 874  
    treatment, 86  
    uric acid metabolism 80 81  
    (rand mal 1151)  
    (ranulocytes eosinophilic 527 See also  
    (ranulocytopenia 12 564  
    Agranulocytosis 564  
    differentiated from aleucemic leucemia 560  
    differentiated from lupus erythematosus  
    disseminatus 1413  
    in acute ulceration of larynx 12  
    in gangrenous stomatitis 46  
    in ulcerative stomatitis 43  
    (ranuloma inguinale 138  
    differentiated from lymphopathia vene-  
    reum 139  
    (ranulomatous lesions 8  
    (rass green sputum 187  
    (ravel nephrolithiasis 194  
    (raves disease See *Goiter exophthalmic*  
    914  
    Great vessels transposition of 4  
    Green sickle See *Chlorosis* 30  
    (La) Gripp See *Influenza* 106  
    (rocco's ar a pleurisy 493  
    Groun litch in arkyotomiasis 04  
    growth hormone 891  
    (humna definition 131  
    (humantated from cancer of the pharynx  
    31

Gumma—Cont d  
 in syphilis 98 131 0 131 1314  
 nervous system 106  
 tongue 39  
 Gum blue line in lead poisoning 1488  
 1489

H

Habit spasms 1004  
 differentiated from chorea 6  
 Hallucinations 1009  
 Hallucinations alcoholic 148  
 Hand Schüller Christian disease See Lipid  
 granulomatosis 9  
 Hand's cirrhosis 750  
 Harelip 32  
 Hailey-Hailey disease See Congenital ichthyosis 148  
 Have hill fever 134  
 Hay fever 144 1446  
 antihistamine treatment 1446  
 Headache from triptamine 14  
 in acidosis 863  
 in acrocephaly 18  
 in acromegaly 32  
 in acute anterior poliomyelitis 1090  
 in disseminated encephalomyelitis 1084  
 in glanders 1340  
 in infectious hepatitis  
 lymphocytic meningitis 106  
 mononucleosis 1402  
 rhinitis 1  
 in African sleeping sickness 1390  
 in anthrax 1388  
 in carbon monoxide poisoning 146  
 in cerebral concussion 1301  
 in choriophthalmitis adenomatous 90  
 in convulsions ergotism 1496  
 in craniofacial angiosarcoma 904  
 in dengue 135  
 in diffuse sclerosis 108  
 in diphtheria 84  
 in duodenal atresia 635  
 in encephalitis St. Louis type of 1085  
 in epidemic cerebrospinal meningitis 1046  
 in encephalitis 108  
 in pleurodynia 1403  
 in erysipelas 130  
 in foot and mouth disease 1344  
 in general hyperkeratosis of hand 1  
 in hydrocephalus 112  
 in influenza 109  
 in intracranial abscess 108  
 in tumors 1124  
 in laryngitis 1406  
 in leptomeningitis 106  
 in low barometric pressure 1440  
 in lymphocytic choriomeningitis 1401  
 in lymphopathia venereum 13  
 in malarial fever 133  
 in meningococcal syphilis 103  
 in migraine 117  
 in motion sickness 1469  
 in mumps 9  
 in nephrotic syndrome 1980  
 in papular fever 1383  
 in plague 1362  
 in pruritus acute flaccid 1088  
 in Q fever 1384  
 in radiation sickness 141  
 in rat bite fever 1347  
 in relapsing fever 179  
 in rheumatoid arthritis 1240  
 in rickets 1469  
 in septemia 1303  
 in smallpox 1393 1396  
 in subdural hemorrhage 110  
 in swineherd disease 136  
 in syphilis 1313  
 in tetanus 136  
 in tsutsugamushi disease 134  
 in tuberculosis meningitis 103  
 in tularemia 133  
 in uremia 11  
 in yaws 132  
 in yellow fever 73  
 post-traumatic cephalalgia 103  
 in intracranial trauma 1104  
 in myeloma 19  
 Heart See also Cardiac  
 aortic disease 188  
 beats auricular fibrillation pulse defect  
 49

Heart beats auricular—Cont 1  
 flutter 390  
 sudden death 393  
 premature 388  
 circulatory disease 34 388  
 pulmonic bifurcated 403  
 trigeminal 403  
 biochemical changes chemo, 34  
 block abortion 400  
 atrioventricular 39  
 auriculoventricular block in diphtheria  
 8  
 Bradycardia 39  
 bundle branch 398  
 complete 396  
 conscious loss of 397  
 coronary arteries disease 46  
 in acute rheumatic fever 9  
 partial 96  
 in auricular block in diphtheria 8  
 Stokes-Adams syndrome 39  
 syncope 9  
 brown atrophy 40  
 cardiac arrhythmias 188  
 enlargement in acute rheumatic fever  
 3  
 digitalis poisoning 39  
 dilatation in diphtheria 8  
 diseased emotional factors and 118  
 diseases 34 1  
 congenital 4 1 4 9  
 aortic group 4 1  
 cardiac lesion diseases of the lung  
 186  
 clubbing of finger and toes 48  
 cor triaculata 4  
 cyanosis 187 4 1 4  
 cyanotic group 43  
 defects of aortic septum, 4  
 diagnosis 48  
 differentiated from esophagotracheal  
 fistula 387  
 incomplete helix rotax 4  
 persistent truncus 4  
 polycythemia 48  
 prognosis 48  
 pulmonary atresia, 4  
 stenosis 43  
 symptoms and signs of  
 transposition of great vessels 4  
 treatment 428  
 x-ray in 48  
 peripheral signs 38  
 pulmonary signs 383  
 disordered action 33  
 displacement of acute nasale pulmon  
 ary collapse 40  
 in lobar pneumonia 31  
 disturbances of rhythm 58 384  
 electrocardiogram, 34  
 enlargement in acute rheumatic fever 8  
 in arteriovenous aneurysm 443  
 in myxoma, 9 4 9  
 extrasystoles in diphtheria 8  
 fatty cell sputum in edema of lung 13  
 in ricin fever 4  
 in scarlet fever 59  
 fatty degeneration of 407  
 infiltration 408  
 gallop rhythm in acute rheumatic fever  
 38  
 in diphtheria, 86  
 in emphysema 11 14  
 metabolic mineral 340  
 in trial disease 148  
 murmurs psychomotoric medicine, 1183  
 muscle physiology See Muscular physiology  
 344  
 myocardial degeneration chronic 40  
 myocarditis acute interstitial 40  
 suppurative 40  
 chronic degeneration 40  
 rheumatic fever 38  
 syphilis 40  
 tuberculosis 406  
 myocardium in acute rheumatic fever 9  
 in rhythmic disturbance 404  
 normal emotional effects on 1183  
 pain precordial 336  
 pericarditis degenerative chronic 40  
 pericardium in rheumatic fever 61

- Heart**—Cont'd  
 peripheral vessels associated with acute  
   rheumatic fever 61  
 phasic lous arrhythmia 348  
 rate in lobar pneumonia 411  
   in septicemia 1303  
 rhythmic fever 561  
 rhythmic disturbances See *Phythetic* *us*  
   *turbances* 384 404  
 rupture of 3 3  
   in coronary arteries disease 4 6  
   lous bradycardia 11 30  
   tachycardia 350  
 small in addition to disease 93  
   in tuberculosis of lungs 304  
 Stokes Adams syndrome 307  
 tachycardia paroxysmal auricular 350  
   ventricular 403  
 tricuspid insufficiency in diphtheria 57  
 valvulitis 3  
   in rheumatic fever 39  
 vasomotor collapse in diphtheria 8 59  
 ventricular premature contraction 400  
 venous circulation 4 0  
   pie sure 4 4  
**Heartburn** 100  
 heat eff. etc. of 14 14 0  
   exhaustion 1100  
   stroke 140  
   sun stroke 14 0  
**Hibernian nodes** See *Osteoarthritis* 1738  
   1 0  
**Hicinc Medica disease** See *Polymyositis*  
   acute anterior 1090  
**Hemachromatosis** 0  
**Hemangioblastoma** 1120  
**Hematemesis** See also *Melena*  
   in anthrax 1 34  
   in carcinoma of liver 33  
   of stomach 610  
   in influenza 111  
   in peptic ulcer 610  
   in tumor of stomach 610  
   in typhus fever 13  
**Hemiparesis** 3 in spinal cord trauma 1100  
**Hemiparesis** in acute glom. rubeophyll 1 60  
   in chronic glom. rubeophyll 1 67  
   in glomerulonephritis 1 1  
   in gonorrhea 13 0  
   in hy. ronephrosis 100  
   in infarcts of the kidney 1 94  
   in influenza 111  
   in nephrolithiasis 1 00  
   in septicemia 1303  
   in subacute bacterial endocarditis 411  
   in tuberculosis of kidney 1 00  
   in tumor of kidney 1 10  
   in typhus fever 13 0  
   renal 107  
**Hemianalgesia** 1017  
**Hemianesthesia** in alternans thermal 101  
**Hemianopia** 990 1000 1009  
 homonymous contralateral in occipital lobe  
   tumors 1131  
   in intracranial abscess 10 8  
   optic chiasm tumors 1130  
**Hemicrania** See *Migraine* 11 7  
**Hemiplegia** 354 947  
   in general paresis 1006  
   in meningococcal septiliasis 10 4  
   in neurophyllia 1063  
   infantile 13  
**Hemochromatosis** 884 88  
   differentiated from Wilson's disease 0 0  
**Hemoglobin** (reduced) 140  
   in anemia 5  
   in cyanosis 179  
**Hemoglobinuria** in acute lead poisoning 1458  
   in malarial fever 13 11  
   paroxysmal 144  
**Hemolytic anemia** sulfonamide toxicity 14  
 jaunice nonf. milil 0 0  
   phenomena See *Jaundice* *chronic* *he* 1  
   lytic 549  
**Hemophilia** 1 0 3  
   anaphylactic shock in 3  
   differentiated from acute rheumatic fever  
   67  
   pseudo hemophilia 3 3  
   in acute rheumatic arthritis 67  
   in serous meningitis 101  
**Hemophilus influenzae** in acute laryngo  
   tracheobronchitis 137  
   in bronchopneumonia 14
- Hemophilus influenzae**—Cont'd  
   in chronic bronchitis 140  
   in influenza 109  
   in septicemia 1 07  
   pertussis in whooping cough 1 1 10 19  
 Hemoptysis See *Hemorrhage* *pulmonary*  
   194  
**Hemorrhage** capillary in cerebral contusion  
   1100  
   cerebral in diabetes mellitus 8 11  
   in osteitis deformans 1 4  
   in vascular lesions nervous system 111  
   1113  
   epidural 1100  
   extradural 110  
   from lungs See *Hemorrhage* *pulmonary*  
   194  
   gastrointestinal See *Melena*  
   in acute hemorrhagic pancreatic necrosis  
   74  
   spirochetal hepatitis 0  
   slow atrophy of liver 12 41  
   in birth injury 1077 1094  
   in bronchiectasis 1 1 6  
   in chronic hepatitis 740  
   in diphtheria 58  
   in intracranial trauma 110 1103  
   in leucemia 1 0  
   acute 101  
   in scurvy 107  
   in spinal cord trauma 1100  
   in subacute bacterial endocarditis 411  
   in thrombocytopenia 170  
   in typhoid fever 100  
   in vitamin C deficiency 95  
   in whooping cough 107  
   in yellow fever 737  
   infarcts in chronic hypoxemia 10  
   into retina in polycythemia vera 101  
   intracerebral in intracranial trauma 10 0  
   1103  
   mucous membranes in anthrax 1338  
   in nasopharyngeal fibroma 1  
   peripheral circulatory failure 3 0  
   pulmonary 194  
   causes 194  
   in acute spirochetal bronchitis 144  
   in bronchiectasis 151 10  
   in chronic bronchitis 14  
   fibrovascular pulmonary tuberculosis  
   0  
   pneumonia 10  
   in foreign body of bronchi 1 0  
   in influenza 109  
   in new growths of bronchi 100  
   in pulmonary diseases 194  
   splinterlike in endocarditis 411  
   subarachnoid in intracranial trauma 10 0  
   1102  
   subdural in chronic meningitis 1077  
   symptomatic 10  
**Henoch's purpura** 100  
   allergic reaction 145  
**Hepatic function** See *Liver function* 15  
   732  
**Hepatitis** associated with chronic glomerulitis 39  
   Hepatitis 31 750 See also *Liver diseases*  
   17 731  
   acute (littoral) differentiated from car  
   cinoma of bile ducts 1  
   infectious 3 33  
   differentiated from chemical intoxica  
   tion 710  
   plasma injection and 7  
   liver function test in 34  
   spirochetal 35 36  
   differentiated from yellow fever 130  
   suppurative 73  
   van den Bergh test 39  
   syphilitic 10  
   arsenic poisoning 13  
   chronic 745 750  
   liver function tests in 48  
   classification 731  
   eclamptic 740  
   in syphilis 1319 13 0  
   infectious differentiated from tsutsuga  
   mushi disease 13 5  
   subacute 740  
**Hepatography** 30  
**Hepato lenticular degeneration** See *Pro*  
   gre lenticular degeneration  
   104  
**Hepatomegaly** in splenic anemia 553





- Hyposecretion 4  
 Hyper sensitivity See *Allergy* 14  
 Hyperthyroidism 114  
 Hypertelism 1790  
 Hypertension 446  
 Hypertension inogen 446  
 Hypertension 444 See also *Blood pressure* 341  
 Differentiated from exophthalmic goiter 917  
 emotional factors in 1157  
 as etiol 444  
 acclasia in 444  
 age in 446  
 arterial hypertrophy 40  
 arteriolar infarction 449  
 basal pressure in 444  
 cardiac dilatation acute 449 44  
 hypertrophy 40  
 cardiovascular system in 44  
 cause 44  
 changed personality 40  
 coronary arteries disease 49  
 course 451  
 diagnosis 44  
 differentiated from lupus erythematosus  
 differential 443  
 Gollblatt's manifestation 44  
 in cardiac failure progressive congestive 39  
 in heart 90  
 in polyarthralgia 31  
 kidney function in 44 44  
 local effects 44  
 malignant 449  
 myocardial failure 449  
 nervous system in 449  
 obesity 440  
 physiological anatomic course 447  
 prognosis 44  
 psychological aspect 1188  
 purpura in 44  
 renal chemistry 448  
 symptomatology 448  
 treatment 44  
 in acute glomerulonephritis 106  
 pulmonary edema 146  
 in bronchitis 40  
 in chronic glomerulonephritis 179  
 in diabetes mellitus 43  
 in glomerulonephritis 106  
 in glomerulo sclerosis intercapillary 1  
 paroxysmal in paragonism carotid  
 gland 90  
 recurrent 446  
 rice diet in 44  
 diet in 44  
 Hyperthermia in gonorrhea 179  
 in thymic ventricle tumors 1130  
 Hypertrophic in differentiated from 100  
 on disease 910  
 diabetes mellitus 43  
 emotional factor in 1109  
 in cardiac failure progressive congestive  
 3  
 in diabetes mellitus 40  
 in dysplasia fibrous 10  
 in exophthalmic goiter 917  
 in nontoxic goiter 913  
 vitamin deficiency 44  
 Hypertonin in epinephrine cerebral venous  
 crisis 1067  
 Hypertrophic interstitial neuritis 100  
 neurofibromatosis 113  
 osteoarthritis See *Clipping of finger*  
 also *Osteoarthritis hypertrophic* 11  
 Hypertrophy idiopathic in congenital heart  
 disease 44  
 Hyperventilation emotional factor 119  
 Hypervitaminosis 806 80  
 Hypohidrosis 973  
 Hypochromic anemia See *Anemia* 1110  
 chronic 53  
 Hypoglycemia coma 1187  
 emotional factors in 1109  
 headache in 802  
 in acute yellow atrophy of liver 4  
 in Addison's disease 93 936  
 in adrenal cortex tumor 91 943  
 in hyperinsulinism 44  
 reaction in insulin administration 844  
 in protamine zinc insulin 43  
 Hypoalcalcaemia—Cretinism  
 severe differentiation from acromegaly in dia  
 betes mellitus 845  
 treatment 843  
 Hypoparathyroidism 948 93  
 endogenous obesity 880  
 Hypomaculosis 11  
 Hypoparathyroidism 940  
 Hypophosphatemia in cellac disease 641  
 Hypophyseal lact tumors 110  
 Hypoproteinemia in glomerulosclerosis inter  
 capillary 11  
 Hypotile congestion of lung 10  
 Hypotension 448 See also *Blood pressure* 341  
 emotional factors in 1159  
 in Addison's disease 93  
 in snake bite poisoning 140  
 Hypothalamic autonomic mechanism psycho  
 somatic disorders 110  
 Hypothyroidism emotional factors in 1199  
 endogenous obesity 880  
 in diabetes mellitus 40  
 secondary 90  
 Hypotonia muscular in amyotonia con  
 genita 1040  
 Hyaline differentiation from chorea 97  
 hyperin uterine 40  
 rabies 1740  
 tetanus 1740  
 tetany 903  
 I  
 Iatrogenic factors psychosomatic medicine  
 110  
 Icterus See also *Jaundice* 5  
 familial hemolytic van den Bergh reaction  
 44  
 in acute catarrhal cholangitis 19  
 in chronic cholangitis 70  
 in circulatory disturbances in liver 1  
 in ectopic hepatitis 40  
 index 43  
 uconitum van den Bergh reaction  
 Idiocy See *Mongolian idiocy* *Amaurosis*  
*familial idiocy* 1038  
 Idiopathic steatorrhea See *Steatorrhea idi*  
*opathic* 641  
 Iliostyneras in allergy 1437  
 Iliosis regional 40  
 ileus paralytic 40  
 Immersion foot 40  
 Immune globulin extract in measles 103  
 Immunity definition 143  
 Imperforate vagina 90  
 Impotence in male 40  
 Indian hemp See *Cannabis indica* 1485  
 In litigation emotional factors in 1101  
 Infantile cerebral plegia 1040  
 hemiplegia 1041  
 paralysis See *Poliomyelitis* acute an  
 terior 1030  
 Incurry See *Scabies* 11  
 splenic anemia See *Kala-azar* 1386  
 splenomegaly See *Kala-azar* 1386  
 tetany 94  
 Infantile 906  
 intestinal 44  
 sexual in Fröhlich's syndrome 507  
 Infection osteitis deformans 14  
 pulmonary 114 107  
 Infarct of kidney 14  
 Infectious aliphatic in scarlet fever 1  
 due to the bite of mammal 1344  
 etiological factor in diseases 10  
 focal asymptomatic 13  
 in acute asplenia 44  
 in bronchiectasis 10  
 in cardiac failure 3  
 in diabetes mellitus 89  
 in foreign bodies of lungs 10  
 in influenza 109 11  
 in parotitis 46  
 in rhinitis 24  
 in scarlet fever  
 in whooping cough 10  
 multiple infection in leptospirosis 80  
 of larynx non specific 1  
 of mediastinum 99  
 renal 144  
 specific 3  
 catarrhal (19  
 in meningitis 106  
 of pharynx 44

- Infectious diseases acute association of  
 acute rhinitis 11  
 cri 13  
 lysis 13  
 symptomatic 10 13  
 factor in neurocirculatory asthenia 3 3  
 granulomata 8  
 Influenza 106 113  
 age in 10  
 Bacillus Influenzae in 106 108 109 14  
 bronchiolitis in 109 111  
 bronchitis in 109 111  
 bronchopneumonia in 109 111 1  
 complications 11  
 course and termination 111 11  
 crisis 13  
 diagnosis 111  
 differential diagnosis 111  
 differentiated from common cold 111  
 dengue 111 1 83  
 measles 10  
 relapsing fever 130  
 mallipox 1 96  
 trench fever 13 1  
 typhoid fever 111  
 undulant fever 111  
 whooping cough 1  
 encephalitis in 111  
 filtrable virus 106  
 H influenzae in acute laryngotracheobron-  
 chitis 13  
 in bronchopneumonia 14  
 us in 106 107 108 109  
 in bronchiolitis 1 0 1 3  
 in chronic bronchitis 146 148  
 incubation period 106  
 infectious lesions 111  
 leucopenia in 106  
 ly 1 13  
 media tinal enphyema and 10  
 meningococcus in 106  
 otitis media in 110 112  
 pandemic 106  
 paranasal sinusitis in 106 110 11  
 pathological anatomy 10  
 Pfeiffer's bacillus in 106  
 pneumococci 106 108 109 110  
 purpura in 111  
 ra hes in 111  
 secondary lesions 110 110  
 splenomegaly in 109  
 Staphylococcus aureus 106 108 109 110  
 113  
 Streptococcus hemolyticus 106 108 100  
 110 113  
 symptoms 109 111  
 synnym 100  
 tachypnea 109  
 treatment 11  
 types 106  
 virus A and B in 106  
 Influenzal bronchitis differentiated from  
 lobar pneumonia 111  
 bronchopneumonia differentiated from lo-  
 bar pneumonia 111  
 meningitis suis nam de lugs 10 3  
 Inguineos *See Esophagus dysphagia func-*  
*ti* 592  
 Inclusion 14 5  
 Insomnia in congenital syphilis 131  
 symptomatic 10  
 Intestinal relation to deelopment 1104  
 Insular scleroma *See Multiple sclerosis* 1140  
 Insul 510  
 action of 8 3  
 aim uction 851  
 adrenergic antagonists to 9 0  
 allergic reaction 8 4  
 clinical unit 8 3  
 coma 838  
 differentiated from acidosis coma 839  
 complications in diabetes mellitus 4  
 glucose oxidation 4 3  
 in diabetic ketosis 846  
 protamine zinc 8 3  
 reaction 8 3  
 reactions 8 3  
 adrenal 8 3  
 hyperglycemia 8 3  
 use of 8 1  
 Intention tremor 990  
 Interapillary glomerulonephritis 8 4  
 Intestinal muscles 51  
 Intermittent claudication in atherosclerosis  
 mans 1004  
 in thromboangiitis obliterans 467  
 Interstitial pneumonia. *See Pneumonia pri-*  
*mary atypical* 5  
 Intervertebral disc dislocation sciatica 1149  
 Intestinal absorption diseases of 6 9  
 distention 6 9  
 in pneumonia 633  
 diverticula 6 9  
 foreign bodies 633  
 inflammation. *See Enterocolitis acute*  
*catarrhal* 668  
 obstruction 6 9  
 alkalosis 6 7  
 differentiated from acute hemorrhagic  
 pancreatic necrosis 6 7  
 diverticula 660  
 parasites 6  
 schistosomiasis 10  
 stasis 633  
 tract inflammatory disease 668  
 tumors 664  
 Intestines larvae diseases of 646 668 *See*  
*also Colon*  
 appendicitis 641  
 carcinoma 664  
 constipation 64  
 diarrhea 64  
 diverticula 6 9  
 functions 646  
 pain 647  
 symptomatology 647  
 tumors 664  
 benign 664  
 malignant 664  
 malabsorption 629  
 digestion 6 9 830  
 disorders of absorption 6 9  
 celiac disease 641  
 idiopathic steatorrhea 641  
 sprue non tropical 64  
 sprue tropical 643  
 distention 641  
 stasis 635  
 diverticula 659  
 duodenal stasis 6 4  
 duodenitis 631  
 function 6 9  
 jejunal ulcer 6 3  
 motor function 630  
 pain in 631  
 peptic ulcer 6 1  
 regional ileitis 6 3  
 symptomatology 631  
 Intraauricular septum defects in congenital  
 heart disease 4  
 Intracranial abscess 10 8 1081  
 lesions differentiated from diabetes mellitus  
 8 3  
 pressure increased in hydrocephalus 11 2  
 trauma, 1078 1101  
 tumors 11 4 1134  
 cerebellum 1133  
 frontal lobe 1130  
 intracranial pressure 11 4  
 metastatic 1130  
 occipital lobe 1131  
 optic chiasm 113  
 parietal lobe 1131  
 pineal gland 113  
 pons and medulla 113  
 low development 11 4  
 symptomatology focal 1130  
 general 11 4  
 temporal lobe 1131  
 third ventricle 113  
 treatment 1134  
 type 11 5  
 Intraspinal tumor 1134  
 Intraventricular septum defects in congenital  
 heart disease 4  
 Intubation diphteria 11  
 iodine hypersecretion 46  
 in thyroid 1321 1322  
 Iodine radioactive in carcinoma of thyroid  
 922  
 in gastric treatment 4 0  
 Iridocyclitis in acute follicular tonsillitis 51  
 in gonorrhea 1331  
 in mumps 96  
 Iritis in chronic paranasal sinusitis 2  
 Iron lung in diphteria 92  
 Irritable heart of soldiers 4 3

- Hyperscretion 40  
 Hypersensitiveness See *Allergy* 14  
 Hypersynchrony 111  
 Hypertelorism 120  
 Hypertensin 440  
 Hypertension 446  
 Hypertension 444 See also *Blood pressure* 341  
 Differentiated from exophthalmic goiter 017  
 Emotional factors in 1147  
 Essential 444  
   acidosis in 560  
   age in 446 4  
   arterial hypertrophy 40  
   arteriolar infarction 440  
   basal pressure in 440  
   cardiac dilatation acute 440 44  
   hypertrophy 440  
   cardiovascular system in 41  
   causes 44  
   changed personality 440  
   coronary arteries increases 40  
   course 441  
   diagnosis 44  
   differentiated from lupus erythematosus 44  
   dieminatus 1413  
   Goldblatt demonstration 44  
   in cardiac failure progressive congestive 35  
   in gout 64  
   in polycythemia vera 41  
   kidney function in 41 44  
   local effects 44  
   malignant 440  
   myocardial failure 440  
   nervous system in 440  
   obesity 440  
   physiologic anatomical course 447  
   prognosis 440  
   psychological aspect 1188  
   purpura in 44  
   renal ischemia 440  
   symptomatology 444  
   treatment 440  
 In acute glomerulonephritis 1766  
   pulmonary edema 168  
 In baciphilum 497  
 In chronic glomerulonephritis 168  
   in diabetes mellitus 43  
   in glomerulonephritis 168  
   in glomerular sclerosis intercapillary 17  
   paroxysmal in paragangliomas carotid gland 00  
   precursor 440  
   rice diet in 47  
   salt in 44  
 Hyperthermia in gonorrhea 1344  
 In third ventricle tumors 1137  
 Hypertrophy in differentiated from Addison's disease 008  
   diabetes mellitus 63  
   emotional factors in 1109  
   in cardiac failure progressive congestive 3  
   in diabetes mellitus 80  
   in dysplasia fibrosa 10  
   in exophthalmic goiter 017  
   in nontoxic goiter 113  
   thiamine chloride deficiency in 40  
   vitamin A deficiency 40  
 Hypertonia in epileptic cerebral meningitis 104  
 Hypertrophic interstitial neuritis 1040  
   neurofibromatosis 113  
   osteochondroplasia See *Clubbing of fingers* also *Osteochondroplasia hypertrophic* 170  
 Hypertrophy idiopathic in congenital heart disease 4  
 Hyperventilation emotional factor 1179  
 Hypervitaminosis 40 60  
 Hypoparathyroidism 960  
 Hypophthalmia in cellulositis 611  
 Hypophthalmic duct tumors 111  
 Hypoproteinemia in glomerular sclerosis intercapillary 17  
 Hypostatic congestion of lung 17  
 Hypotension 458 See also *Blood pressure* 341  
   emotional factors in 1180  
   in Addison's disease 03  
   in snake bite poisoning 140  
 Hypothalamic autonomic mechanism 1130  
   anatomic disorders 1119  
 Hypothyroidism emotional factors in 1190  
   endogenous obesity 80  
   in diabetes mellitus 80  
   secondary 070  
 Hypotonia muscular in amyotonia congenita 104  
 Hysteria differentiated from chorea 07  
   hypnotism in 80  
   rabies 114  
   tetanus 174  
   tetany 071  
 I  
 Intrinsic factors psychosomatic medicine 110  
 Icterus See also *Jaundice* 776  
   familial hemolytic van den Bergh reaction 4  
   in acute catarrhal cholangitis 68  
   in chronic cholangitis 11  
   in circulatory disturbances in liver 1  
   in eclamptic hepatitis 40  
   index 6 33  
   neonatorum van den Bergh reaction  
 Idiocy See *Mental idiocy* *Amaretotic*  
   family idiocy 1038  
 Idiopathic tetanospasmosis See *Tetanospasmosis idiopathic* 641  
 Illicit drugs in allergy 1437  
 Iliac regional 4060  
 Iliac paralytic 4  
 Immerion foot 43  
 Immune globulin extract in measles 103  
 Immunity definition 1417  
 Imperforate vagina 10  
 Impotence in male 01  
 Indian hemp See *Cannabis indica* 1480  
 In litigation emotional factors in 1101  
 Infantile cerebral palsy 1040  
   hemiplegia 1041  
   paralysis See *Polio-myelitis acute and*  
   tetanus 1090  
 Scurvy See *Scurvy* 80  
 Splenic anemia See *Kala-azar* 1386  
 Splenomegaly See *Kala-azar* 1386  
 Tetanus 04  
 Infantile 006  
   intestinal 42  
   sexual in Fröhlich's syndrome 50  
 Infarction osteitis leformans 14  
   pulmonary 194 109  
 Infarct of kidney 184  
 Infection diphtheritic in scarlet fever 1  
   due to the bites of mammals 144  
   etiological factors in measles 10  
   focal symptomatic 13  
   in acute saladenitis 46  
   in bronchiectasis 1  
   in cardiac failure 3  
   in diabetes mellitus 80  
   in foreign bodies of lungs 1  
   in influenza 109 112  
   in parotitis 40  
   in thymus 4  
   in scarlet fever  
   in whooping cough 14  
   multiple lesions in lightening 4  
   of larynx non specific 1  
   of mediastinum 109  
   renal 174  
   specific 1  
   enterocolic 109  
   in meningitis 106  
   of pharynx 4

## Larynx—Contd

- paralysis of 119 1
- polyps 131 13
- singers nodule 1 4
- spasm in 1 0
- syphilis of 130 131
- diagnosis 131
- differentiated from carcinoma of larynx 131 13
- simple laryngitis 131
- tubercle of larynx 1 9 131
- dyspnea in (strictly of) 131
- tumors in 131
- carcinoma in 131
- prognosis 131
- symptoms 131
- treatment 131
- tuberculosis of 1 9 130
- diagnosis 1 9
- differentiated from laryngeal carcinoma 1 9 13
- lupus 1 9 130
- syphilis 1 9 131
- prognosis 130
- symptoms 1 9
- treatment 130
- tumors 131 13
- Local 1487 1491
- cult 1488
- in epipharynx 1488 See also Lead poisoning 1488 and Laryngitis lead 1488
- differs from brain tumors 1140
- in uritis 109
- Local 1489
- poisoning 1487
- acute 1488
- boophilic granulation 1488 1489
- blood change 1488 1489
- calcium diet in 1491
- chronic 1488
- diagnosis 1488
- gastrointestinal system 1488
- gout and 1488
- gun's blue line 1381 138
- hematological system in 1488
- in children 1489
- lead encephalopathy 1140 1488 1489
- nervous system in 1489
- treatment 1488
- portal of entry 1487
- Leber's disease See Atrophy optic primary hereditary 10 1
- Leishmania brasiliensis in cutis 1386
- donovanii in kala-azar 1386
- tropics 1386
- in Oriental sore 1384
- Leishmania in 1384
- Lemon yellow tint to skin in pernicious anemia 37
- Leontia in See Hyperkeratosis of skin 1 7
- Leprosy 1404 1409
- anesthesia 1406 140
- atrophy of face 140
- Bacillus leprae 1404
- chaulmoogra in 1408
- claw nails 1407
- diagnostic diagnosis 1408
- diagnosis in 1407
- geographical distribution 1404
- leone appaance 1407
- mucocutaneous nodular 1406
- mucous membranes 140
- nails in 1407
- nervous system 1405
- neural or anesthetic 1406 1407
- nodular 1406
- nose infection in 3
- pharynx, 29
- differentiated from lupus pharynx 9
- pigmentation 1407
- portal of entry 1404 1406
- prognosis 1408
- prominent in 1409
- rhinitis in 1406
- skin in 140 1406
- symptoms 1405
- syringomyelia 140 1408
- treatment 1408
- tubercular 1406
- X-ray therapy 1409

## Lithomycetis 1065

- Lipoma lipoatrophy 73
- lethargy in epidemic encephalitis 108
- in whooping cough 1 8
- Leucemia 4 9 Leucemia 5 3
- Leucemia 5 3 64
- cult 560 6
- anatomical findings 61
- anemia in 560 561
- blood examination 61
- differentiated from agranulocytosis 6
- diphtheria 58
- epidemic of lenticular tonsillitis 1
- hemorrhages in 61
- lymphatic differentiated from tularemia (glarular type) 133
- plenumegaly 561
- symptoms 560
- aleucocytosis 9
- differentiated from aleucemic reticulosis 5 6
- granulocytopenia 560
- Hodgkin's disease 583
- anatomical findings 55 57
- nemia 5 5
- blood examination 565
- culture in 5 7
- diagnosis 7
- differentiated from Bant's disease 5 7
- hemolytic jaundice 57
- Hodgkin's disease 557
- lymphoma 557
- pernicious anemia 7
- differentiation in 53
- infectious 64
- fever in 5 5
- in children 62
- lymphatic chronic 53
- infectious 5 5 563
- blood examination 62
- infectious chronic 555
- symptoms and signs 5
- syndrome 3
- trombo 5 55
- treatment 557
- depression 557
- urine in 55
- Leucemic infiltration 5
- with ulceration differentiated from leprosy 1408
- Leucocytes
- diagnosis of 5 3 64
- Leucocytopenia See Leucemia 563
- Leucocytosis in acidosis 538
- in acute catarrhal cholecystitis 59
- follicular tonsillitis 51
- hemorrhagic and pancreatic necrosis 4
- massive pulmonary collapse 54
- rheumatic fever 57
- suppurative cholangitis 69
- in bronchopneumonia 218
- in chronic fibroclastic pulmonary tuberculosis 96
- tonic 51
- in epidemic cerebrospinal meningitis 1068
- follicular tonsillitis 52
- erysipelas 1306
- in infection of kidneys 1289
- in leucemia 53
- lobar pneumonia 231 41
- in lupus erythematosus and seminatus 141
- in malarial fever 139
- in new growth of bronchi 168
- in paratyphoid acute flaccid 1089
- in peritonitis 505
- in fever 1361
- in rat bite fever 1349
- in scarlet fever 3 30
- in septicemia 1401
- mononuclear in acute mononucleosis 1402
- polymorphonuclear in chronic pneumonitis 5
- in elephantiasis 1381
- in intra-abdominal abscess 1078
- in plague 1362
- in relapsing fever 1360
- in smallpox 139
- in swine fever 1356
- Leucopenia antibiotic therapy 143
- clonotherapy 14 3
- in aplastic anemia 546
- in denature 138 1383

- Irritability in epidemic encephalitis 108  
 in retropharyngeal abscess 29  
 in simple stomatitis 34  
 Irritating gases in acute tracheobronchitis  
 134 147  
 particles in acute tracheobronchitis 131  
 147  
 in chronic bronchitis 141  
*Ischemia myocardial* 406
- J**
- Jacksonian epilepsy 1009 1120 1125 See  
 also *Epilepsy* 1150  
 Jaki fever See *Typhus fever* 1351  
 Japanese river fever See *Tsutsugamushi*  
*disease* 354  
 Jarisch Herxheimer reaction in syphilis 13  
 Jaundice See also *Icterus* 6  
 acholuric chronic See *Jaundice; hemo-*  
*lytic chronic* 343  
 congenital nonobstructive 49  
 acute catarrhal See *Hepatitis acute in*  
*fectious* 37 735  
 epidemic See *Hepatitis acute infectious*  
 32 135  
 familial chronic See *Jaundice hemolytic*  
*chronic* 49  
 hemolytic chronic 349  
 differentiated from leukemia 44  
 subacute hepatitis 744  
 familial differentiated from splenic  
 anemia 52  
 nonfamilial 50  
 secondary 649  
 in acute catarrhal cholangitis 63  
 infectious hepatitis 732  
 yellow atrophy of liver 41  
 in granulocytosis 56  
 in arsenic poisoning 149  
 in biliary obstruction 8  
 in carcinoma of liver 53  
 of pinna 6  
 stomach 619  
 in chemical intoxication 40  
 in cholelithiasis 63 66  
 in chronic arterial poisoning 149  
 hepatitis 747  
 in influenza 111  
 in malaria 101  
 in obstructive hepatic cirrhosis 9  
 in septicemia 1303  
 in syphilis 10 1309  
 in yellow fever 3  
 Jejunal ulcer 63  
 gastro jejuno colic fistula 63  
 Joints diseases of 1 3 1 58  
 in acute rheumatic fever  
 in osteoarthritis 149 1  
 in rheumatoid arthritis 140 14  
 Juvenile arthritis Reformer 14
- K**
- Kallers disease See *Myeloma multiple*  
 1126  
 Kahn reaction in syphilis 1319  
 Kalazar 1286 1339  
 Kalazar disease See *Tsutsugamushi disease*  
 134  
 Keratitis in acute follicular conjunctivitis 51  
 in influenza 111  
 in measles 101  
 in tonsillitis 51  
 in tularemia 1336  
 syphilitic in congenital syphilis 1318  
 Kernig's sign in acute meningitis 1309  
 Kymocytic meningitis 10 6  
 in leptomenigitis 106  
 Ketogenic diet in epilepsy 11  
 Ketone bodies 8  
 Ketosis See *Acidosis* 86  
 Kidney artificial 1781  
 kidneys See also *Renal function* 1  
 adrena cortical 1 89  
 treatment 1 91  
 amyloid disease 1 83  
 carcinomata 1296  
 congenital aplasia of 1 83  
 cystic differentiated from tumor 1 81  
 neoplasms 1 87  
 polycystic 1 83
- Kidneys—Cont 1*  
 embryomata 196  
 function See also *Renal function* 195  
 excretion of foreign substances 1261  
 in acute yellow atrophy of liver 742  
 in essential hypertension 451  
 in gout 16  
 in hypernephromata 1  
 infarction 1 84  
 infections 1 88  
 sarcomata 1 96  
 lesions in acute rheumatic fever 64  
 syphilis 1 90 192  
 tuberculosis 1 90  
 tumors 1 91  
 Limpke's palsy 1099  
 Koplik's spots differentiated from leucocyto-  
 sis scarlet fever 30  
 measles 99 100 10  
 Korakoff's psychosis 14 9  
 alcoholic polyneuritis 1095  
 Krause's vitamin deficiency 8  
 Kummel's disease 1107  
 Kusmaul's respiration See *Acidosis* 864  
 Kyphosis in acute anterior poliomyelitis 1091
- L**
- Labyrinthitis acute differentiated from in-  
 tracranial abscess 109  
 Laceration in local and systemic diseases  
 19 90  
 in whooping cough 195  
 Lactogenic hormone 891  
 Lactones cirrhosis See *Hepatitis chronic*  
 4  
 Laminectomy in chronic adhesive arachnoidi-  
 tis 10 8  
 Landry's paralysis See *Paralysis acute*  
*ascending; flaccid* 1088  
 Lange reaction asymptomatic neurosyphilis  
 10  
 Laryngeal paralysis in exophthalmic goiter  
 318  
 in nontoxic goiter 91  
 in lobar pneumonia 39  
 ulceration in tuberculosis of lungs  
 Laryngismus stridulus diagnosis 120  
 differentiated from acute laryngotracheo-  
 bronchitis 137  
 in tetanus 96  
 symptoms of 1 1  
 Laryngitis chronic 1 3  
 diagnosis of 1 4  
 in bronchitis chronic 148  
 in influenza 109  
 in lobar pneumonia 39  
 in measles 100  
 in whooping cough 1 6  
 larynx 1  
 simple differentiated from syphilis of  
 larynx 131  
 tuberculous in chronic fibrovascular pul-  
 monary tuberculosis 99  
 Laryngotracheobronchitis acute 137  
 diagnosis 131  
 Larynx 119 13  
 and bronchial system 115 177  
 anatomy 119  
 carcinoma 137  
 differentiated from syphilis of larynx 13  
 tuberculosis of larynx 129 13  
 congenital trismus of infants 1 1  
 diseases cough in 116  
 symptoms 1 3  
 disturbance of phonation 11  
 edema of 1 3  
 fibroma 1 111  
 functional aphonia 1 9  
 disorders 191  
 hyperreflexia in 1 9  
 in diphtheria 83 85  
 infections acute catarrhal 1  
 ulcerative 1  
 associated with granulocytopenia 122  
 specific 1 4 13  
 intubation of in diphtheria 92  
 laryngismus stridulus 1 9  
 laryngeal edema of inflammation 141  
 lupus 1 9 130  
 myeloma 1 9  
 obstruction cyanosis in 18  
 papilloma 1 131



## Leucopenia—Cont 1

- in diphtheria 108
- in Friedländer's pneumonia 3
- in influenza 109
- in kala azar 1387
- in lupus erythematosus disseminatus 141
- in lymphocytic choriomeningitis 1401
- in malarial fever 1314
- in measles 89 100 10
- in papular fever 1393
- in paratyphoid fever 681
- in pernicious anemia 39
- in radiation sickness 1411
- in salmonella ulcerifer infection 69
- in splenic anemia 3
- in tuberculosis miliaris 34
- in typhoid fever 681
- in ulcerative stomatitis 43
- in uninfant fever 693
- penicillin in 1433
- sulfonamides in 1433
- Wray 141

## Leucoplakia buccalis 38

- vitamin deficiency 85
- Leucorrhea emotional factors in 100
- Leucose test in carbohydrate metabolism 29

## Leuotitis also lesions 142

- in acute laryngotracheobronchitis 140
- mustard gas compared with 141
- protective measures 141

## Lobular nodules in subacute bacterial endocarditis 411

## Lentheric diarrhea see Diarrhea lenteric 558

## Lightning effects see Electric shock light 14 3

## Lightning palsy tabes dorsalis 1038

## Lightning rock 351 14 3

## Lindau's disease intracranial tumor 11 9

## Lipemia in diabetes mellitus 8 2

## Lipoid in bronchiectasis 164 8 5

## in bronchogenic carcinoma 161

## in chronic adhesive arachnoiditis 1078

## bronchitis 146 148

## pneumonia 68

## spinal arachnoid space 1035

## Lipodystrophy progressiva 884

## Lipoid celled pneumonia see Pneumonia

## lipoid 4

## granulomatous 9 581

## histiocytosis 518 579

## pneumonia see Pneumonia lipoid 4

## Lipomatosis 881 884

## lips carbuncle 3

## dermatitis oris 3

## eczema 35

## herpes oris 3

## staphylo of 37

## Listeria monocytogenes in acute mononucleosis 1402

## Little's disease see Infantile cerebral dis 1046

## Liver see also Dile

## acute yellow atrophy 42

## Babinetski sign 74

## blood chemistry 74

## diet in 744

## hemorrhage in 42 43

## hypoglycemia 4

## pathological anatomy 4

## renal function 42 742

## symptomatology 41

## treatment 44

## wine in 74

## vasoparalysis 743

## amebic abscess differentiated from malaria 13

## anomalies 21

## ascites 1

## carcinoma metastatic 3 7 4

## primary 51 53

## symptoms and signs 53

## chemical intoxications 39 740

## circulation 715 21

## cirrhosis differentiated from splenic anemia 553

## in progressive cuticular degeneration 1045

## van den Bergh reaction 24

## cyst 54

## degenerative lesion 39 754

## diabetes mellitus 816

## diffuse syphilitic cirrhosis 4

## Liver—Cont 1

- diseases of 731 7 4
- anemia in 22
- biliary cirrhosis 750
- bronze liver 3 0
- chemical intoxications symptomatology 739

## Hansen's cirrhosis 7 0

## hemachromatosis 0

## pigment cirrhosis 150

## echinococcus cysts 4

## tumors of abdominal viscera 17

## enlargement in acute pyrochetal hepatitis 73

## in acute wat berriess 181

## in hemochromatosis 884

## in kala azar 1381

## in lymphopathia venereum 13 8

## function 1 31

## bile secretion 3

## carbohydrate metabolism 21

## cells Küttler 717

## stellate 17

## degenerative lesions 29

## detoxicating 1

## dye tests of hepatic function 9

## fat metabolism 3

## flocculation tests 7 9

## glycogen storage 1

## hematologic 28

## hippuric acid test in 6

## mineral metabolism 3

## portal stasis 17

## protein metabolism 7 7

## tests 1

## jaundice see also Jaundice

## acute yellow atrophy 11

## in chemical intoxications 740

## obstruction see Biliary obstruction 7 8

## palpable in acute infectious hepatitis 123

## pigment cirrhosis see Brown's diabetes 881 883 and Hemochromatosis 884 88

## secondary hepatic diseases 4

## syphilis 50 11

## treatment 51

## tumors 51 54

## benign 1

## carcinoma 51 4

## classification 51

## cystic 744

## malignant 1

## solid 1 34

## Living organisms susceptibility to aureomycin 1431

## to penicillin 1430

## to streptomycin 1431

## to sulfadiazine 1430

## to sulfaguanidine 1430

## Lobar pneumonia see Pneumonia lobar 6 255

## sclerosis see Luck's disease 1138

## Lobelia diaca see Ostrya diaca super 1715

## Lockjaw see Tetanus 1341 1344

## Locomotor ataxia see Tabes dorsalis 1038 106

## as tem diseases of 1 05

## emotional factors in 1 01

## Lone star fever see Ehrlich's fever 1364

## Lower nephron nephrosis 1 84 1 85

## Ludwig's angina 4

## Lues see Syphilis 120

## Lumbago 1244

## in gout 8 6

## Lumbar puncture 10

## Luminal in epilepsy 1155

## Lungs see also Pulmonary

## abscess 163

## in bronchiectasis 1 6

## in chronic pneumonia 267

## in phthisis tubercular 301

## necrosis 319

## alveolar gaseous interchange 1 8

## alveoli in 118

## anoxemia arterial in 1 8

## a periglottis 3 0

## atelectasis see Pulmonary atelectasis 199 0

## atelectatic lungs in new growths 1 8

## benign lympho-ranuloma 314

## blastomycosis 318

## Boeck's sarcoid 314

## cardiac arrhythmias 188



Lung — cont'd  
 circulation 18;  
 circulatory disturbance 190  
 cause of 190  
 pathological anatomy 191  
 symptom 18  
 treatment 199  
 cirrho of See Jaen (corros) 1  
 coecidiosis 118  
 collagen disease in chronic pneumonia 6  
 cryptococci 319  
 croup bronchial asthma 183  
 bronchitis 183  
 bronchopneumonia 184 185  
 ciliary factor 181  
 clinical condition 18  
 congenital cardiac 181  
 carbon dioxide 18  
 laryngeal and tracheal obstruction 18  
 lobar pneumonia 18 34 3 1  
 local cause 18  
 pneumonia 183  
 pulmonary 18 a 186  
 rate of blood flow 181  
 respiratory factor 180  
 tuberculosis of lung 88  
 cysts of 1 9 163  
 acquired 189  
 bronchogenic carcinoma 161  
 congenital 1 9 160  
 hilarity of bronchi 160  
 term 160  
 differentiated from bronchiectasis 163  
 echinococci 18  
 emphysema 160  
 inflammation 160  
 bronchiectatic cavity 163  
 bronchoectatic cavity 163  
 muco 160  
 pulmonary pneumatocoele 163  
 teratomata 160  
 treatment 16  
 disease of 118  
 atelectasis See Pulmonary atelectasis 1  
 199  
 benign lymphogranuloma 314 317  
 bronchopneumonia See Bronchopneumonia 109 14 3  
 circulatory disturbance 190  
 cyanosis 19  
 dyspnea 189  
 edema 190  
 reduced hemoglobin 19  
 signs 189  
 symptomatology 19  
 edema 118 190 194  
 in asthma 1448 1449  
 emphysema See Emphysema 0  
 exudate in new growth 190  
 fibro 18  
 in new growth 190  
 foreign body See Foreign body 1  
 gangrene in bronchiectasis 16  
 glottis 3 1  
 granulomatous lesions 8  
 hemorrhage See Pulmonary hemorrhage 194  
 histology 319  
 hydatid disease 3 1  
 hypertensive acute pulmonary edema 166  
 hypotatic congestion 19  
 in lymphogranuloma benign 314 31  
 infection of diabetes mellitus 83  
 mass cellular in chronic pneumonia 6  
 mitral stenosis acute pulmonary edema 166  
 moniliasis of 0  
 mucous of 3 1  
 nictitating membrane of 3 1  
 pneumonia of 3 1  
 pneumothorax a fissure 18  
 pulmonary edema 190  
 signs of 189 88  
 of new growth 189  
 plethorism of 3 1  
 tracheitis 321  
 tracheitis of respiratory obstruction 189  
 sphincter of 31  
 tuberculous (See 31 See also Pulmonary tuberculo 8

Lung tube of — Cont'd  
 age in 81  
 aortic valve on 88  
 bacteriological examination 90  
 (affix) 91  
 bronchitis in 89  
 cause of agent 8  
 cavitation in 89  
 chronic fibrotic rat 96 49  
 hilar 90  
 clinical for and course of 9 92  
 condition in 89  
 cough in 8  
 cyano in 88  
 let of pulmonary on 88  
 different from bronchiectasis 11  
 new growths of bronchi 10  
 lymphatic 88  
 edema in 88  
 exophthalmic goiter 91  
 fever in 83 9  
 fibr 59  
 (affix) case 91  
 heart nail in 204  
 hemunimolical examination 91  
 hemostasis 8  
 in children 94  
 in diabetes mellitus 81 83  
 in neck 81  
 in whooping cough 81  
 incidence 81  
 incubation period 81  
 infection 81 84  
 infiltration 289  
 Mantoux reaction 81 82 9  
 military 84  
 acute 93 9  
 chronic 9 96  
 night at 86  
 on 83 96  
 pain in 88  
 pathological anatomy 84 88  
 physical examination 88  
 portal of entry 8  
 primary infection 84 9  
 resistance of individual 281  
 condensation 8  
 signs of lesions in 189 88  
 local tattoo 81  
 sputum in 8 90 96  
 symptom and sign focal manifestation 8  
 systemic manifestation 88  
 synovium 8  
 tachycardia 86  
 treatment 30 31  
 tubercle bacilli 8  
 human organism 80  
 resistance 8  
 in physical examination 90 93  
 Lymphatic examination 90 93  
 blood in 141  
 cardiac valve system 141  
 ligament 141  
 skin lesion 141  
 larynx 10  
 differentiated from tuberculosis of larynx 19 120  
 nasopharynx 4  
 pharynx 8  
 differentiated from larynx 9  
 pharynx 9  
 lymphatic cervical enlargement in acute 51  
 of acute mononucleosis 140  
 disease of 141 58  
 malignant African sleeping sickness 139  
 in anthrax 13 8  
 in chancroid 11 4  
 in mumps 3  
 lymphoplasma in measles 101  
 malignant differentiated from new growth of bronchi 10  
 in new growth of bronchi 167 168  
 in enlarged See also adenopathy 8  
 enlargement 43  
 Lymphadenitis differentiated from Hodgkin disease 583  
 in turgidum d sea e 13 4

- lymphadenopathy in African sleeping sickness 1390  
 in rheumatoid arthritis 1240  
 lymphangitis acute septic differentiated from elephantiasis 1381  
 in glanders 1340  
 in rat bite fever 134  
 in tularemia 1336  
 lymphatic glands See *Lymph glands diseases* of 581  
 lymphocytes 59  
 lymphocytic choriomeningitis 1401  
 lymphocytosis in mumps 90  
 in rubella 100  
 in whooping cough 1617  
 mononucleosis 140  
 lymphogranuloma benign 31431  
 of lung 314  
 lymphogranulomatosis See *Hodgkins disease* 81  
 benign See *Lymphopathia venereum* 132  
 inguinalis See *Lymphopathia venereum* 13  
 lymphomata salivary glands 49  
 lymphopathia venereum 130  
 blood filling in 138  
 differential diagnosis 1328  
 differentiated from syphilis 1308  
 Fiel test 138  
 groin glands enlarged 137  
 periauritis 139  
 symptoms and signs 137  
 synonym 13  
 treatment 138  
 lymphopenia in rat bite fever 1340  
 lymphorhachis mya thenia gravis 1140  
 lympho sarcoma 3034  
 anatomic findings 94  
 differentiated from aleucomic reticulosis 96  
 Hodgkins disease 583  
 leucemia 97  
 new growth of bronchi 11  
 symptoms 84  
 lysis 13 100  
 Lysa See *Fabies* 1345
- M
- Macrognathia precox 967  
 Macroglossia 39  
 Maladie de Bouchet See *Siccinhera disease* 1365  
 Malaise in acute follicular tonsillitis 1  
 rheumatic fever 1  
 in chorea 69  
 in diphtheria 84  
 in mumps 90  
 in whooping cough 17  
 Malaria. See also *Malarial fevers* 1266  
 crisis 13  
 differentiated from pulmonary tuberculosis 130  
 differentiated from typhoid fever 686  
 in herpes oris 20  
 lysis 13  
 tertian 160 133  
 treatment general paresis 1009  
 Malarial fever 130 138  
 active autumnal 1300 139  
 algid type 134  
 associated with herpes oris 20  
 blood count in 14  
 chills character of 133  
 comatos type 134  
 differential diagnosis 130  
 amebic abscess of liver 135  
 endocarditis subacute bacterial 137  
 Kala azar 1288  
 miliary tuberculosis 13  
 rat bite fever 1349  
 relapsing fever 130  
 trench fever 1356  
 tsutsugamushi disease 13  
 tularemia (typhoid type) 1337  
 typhoid fever 135  
 typhus fever 1353  
 hemoglobinuria in 139  
 hemorrhagic type 134  
 herpes labialis 133  
 laboratory examination 130  
 malarial cachexia 134
- Malarial fevers—Contd  
 parasites differential characteristics of 1613  
 pathological anatomy 134  
 plasmodium in 134  
 plasmodium falciparum 136 138  
 plasmodium malariae 136  
 plasmodium vivax 136  
 quartan 136  
 quinine in 13 136  
 quotidian malaria 133  
 relapse in 13  
 plenomenia in 133  
 symptoms and signs 133  
 synonyms 136  
 tertian 136 133  
 treatment 130  
 Malarial 136  
 Male gonads abnormalities of 940  
 Malignant exanthema 1  
 Malignant pustule See *Anthrax* 1337  
 Mallocomyces mallei 1339  
 Malleus See *Glanders* 1329  
 Malnutrition 18  
 chronic 50  
 Malta fever See *Undulant fever* 693  
 Mantoux test in tuberculosis of lungs 91  
 Marble bones See *Osteopetrosis* 1217  
 Marginal ulcer See *Jejunal ulcer* 63  
 Marie Strömberg type of rheumatoid arthritis 141  
 Marie ataxia See *Ataxia cerebellar hereditary* 1043  
 disease See *Osteoarthropathy hyper trophic* 10  
 Marijuana See *Cannabis indica* 1485  
 Marasmus coxae senilis 101  
 Massive pulmonary collapse acute 100  
 chronic 150  
 pneumonia chronic 90  
 cystitis from mumps 90  
 Mastoiditis acute in serous meningitis 1077  
 differentiated from epidemic cerebro spinal meningitis 10  
 in intracranial abscess 108  
 Measles 90 104  
 acute encephalitis in 10  
 adenitis in 101  
 a renal in weakness 913  
 angina differentiated from diphtheria and  
 ring 58  
 bronchiectasis in 101 100  
 bronchiolitis in 101  
 bronchitis in 101  
 bronchopneumonia 101 101  
 causative agent 9  
 complications 101  
 cornea in 97 95 100  
 crisis 13 103  
 duration in 100  
 eruption in 10  
 differential diagnosis 90 84 10 10 1  
 differentiated from common cold 99 10  
 diphtheria 84 10  
 influenza 100  
 Rocky Mountain fever 19  
 rubella 100  
 scarlet fever 80 100  
 eruption disease 1433  
 smallpox 130  
 typhoid fever 10  
 typhus fever 133  
 whooping cough 17  
 enlarged spleen in 99  
 eruption 90 100 10 104  
 differentiated from scarlet fever 100  
 eye 103  
 hyperpyrexia 104  
 in bronchiectasis 10 103  
 in chronic bronchitis factor in 146 149  
 incubation period 94  
 jaundice in 101  
 Koplik spots 90 100 100  
 laryngitis in 100  
 leucopenia in 80 100 10  
 lysis 13  
 mucous membrane in 93  
 otitis media in 10  
 panophthalmitis in 101  
 pathological anatomy 98  
 photophobia in 103  
 pleurisy in 101  
 pneumonitis in 101 104

## Measles—Cont'd

- red prodromal stage 98
- purulent conjunctivitis in 101
- rash in 99 100
- differentiated from scarlet fever rash 10-
- prodromal 100
- respiratory system 100
- splenomegaly in 99 101
- symptoms 99
- synonym 9
- treatment 103 104
- tuberculosis in 10 251
- tuberculous meningitis in 10
- virus 99
- Meckel's diverticulum 60
- Melioidosis acute 10
- Mediastinitis acute suppurative 10
- chronic 9 10
- new growths 1
- Mediastinum diseases of 99 10
- mediastinal emphysema acute 510
- mediastinitis acute nonsuppurative 99
- 10
- chronic 510
- adhesive differentiated from new
- growths of bronchi 11
- new growths 1
- purulent in lobar pneumonia 29
- displacement in lobar pneumonia 31
- tumors 11
- Mediterranean fever See Undulant fever 693
- Medulla tumor 113
- Metastases 11
- Megalocephalus See Hyperkeratosis of skull
- 1
- Megalocolon with atarrhea 84
- Melancholes mumps as cause of 96
- Melena in melicoid enteritis 90
- in anthrax 1339
- in bacillary dysentery 173
- in carcinoma of colon 664
- of stomach 619 620
- in chronic hepatitis 46
- in gastric ulcer 110 61
- in influenza 111
- in jejunal ulcer 63
- in pellagra 9
- in scurvy 97
- in splenic anemia 53
- in typhoid fever 64
- in typhus fever 13
- in undulant fever 694
- Meningitis 10
- in cerebral concussion 1101
- asymptomatic 10
- Meningitis of base See Ventral system
- cranial nerves eighth auditory
- 1094
- Meninges anatomy 947
- pyogenic infection 104
- Meningiomas 1127
- Meningitis 1047 106
- acute a pyogenic See Meningitis acute lymphocytic
- 1076
- lymphocytic 10 6 10 7
- differentiated from acute mononucleo-
- sis 1403
- synonyms 1076
- syphilitic See Cerebrospinal syphilis
- 1051 1055
- benign See Meningitis acute lymphocytic
- 1076
- cerebral vascular disease 111
- chronic meningococci 1049
- posterior basal 1049
- recurrent meningococci 1049
- differentiated from military tuberculosis
- 99
- differentiated from serum disease 14 9
- differentiated from tetanus 144
- epidemic cerebrospinal 1046
- bacterial 1067
- blood examination 10 0
- carrier 10 0 10
- complicated 1069
- courtesy in 1071
- diagnosis 10 0
- differential diagnosis 10 0
- differentiated from Rocky Mountain
- fever 13 5
- differentiated from smallpox 1 96
- typhus fever 133 133
- hypocercic 1049
- in influenza 1076
- Kernig and Brudzinski signs 1067

## Meningitis epileptic cerebrospinal—Cont'd

- meningeal lesion 106
- stage 10 10 0
- meningococci 1046
- nasopharyngitis in 1066
- onset 1066
- pathological anatomy 1069
- prognosis 10 0
- prophylaxis 10
- septicemia 106
- epileptic phase 10 0
- kin manifestation 106
- spinal fluid 1069 10 0
- splenomegaly 1066
- symptoms 1066
- synonyms 1066
- treatment 10 1
- sulfonamide in 10 1
- types 106 104
- in bronchitis 104
- in chronic fibrous keratitis and pulmonary tuber-
- culosis 103
- in epileptic follicular tonsillitis 3
- in influenza 111 10 0 10
- in mumps 96
- influenza nitrite reaction in 10
- pneumococcal cerebrospinal fluid 10 4
- pyelotrophic See Douchard's disease
- 1364
- secondary causes 10 4
- serous 10
- differentiated from intracranial abscess
- 10 9
- sterile See Meningitis Serous 1077
- streptococcal 10 4
- syphilitic 1043
- acute 104
- differentiated from tuberculous meningitis
- 10 4
- tuberculous 10 3
- in measles 10
- various types 10 8
- Meningocele 1047
- Meningococci in septicemia 130
- Meningococcal meningitis See Meningitis
- epidemic cerebrospinal 1066
- Meningoencephalomyelitis 1068
- Meningomyelitis 1044 1068
- Meningo-vascular syphilis 1043
- Meningitis 94
- Menorrhagia 1
- in chronic 89
- Menstruation 94 9 6
- disturbances of 10
- Mental deficiencies 103
- in acute yellow atrophy of liver 41
- in African sleeping sickness 1 90
- in diffuse sclerosis 105
- in epidemic encephalitis 104
- in intracranial abscess 10 8
- tumors 112
- in Pelliculus Merzbacher disease 1039
- in tuberculous sclerosis 1044
- excitation in rabies 134
- in typhus fever 133
- retardation See Mental deficiency 1037
- Mercurial compound 77
- Mercury hypersecretion 46
- in syphilis reaction to 13-3
- poisoning 111 114
- cause of chronic parotitis 47
- Vesicular arteries 4
- thrombosis differentiated from acute hem-
- orrhage pancreatic necrosis 4
- Metabolic and nutritional disorders in car-
- diac failure 107
- disturbances and dyspepsia 3 6
- Metabolism and endocrine system psycho-
- sonic medicine 1104
- biological in exophthalmic goiter 110 91
- lowered in Prothrombin Iron 10
- lowered in thyroid disease 101
- rate increased in nodular goiter 916
- lowered in thyroid goiter 919
- calcium 100
- carbohydrate 1
- endocrine glands in 113
- in diabetes mellitus 113 1 5,3
- central nervous system thiamine deficiency 86
- diagnosis of 109
- emotional factors in 1159



My laminectomy 1077  
Myocardial changes in nodular toxic gutter  
913

degeneration 49  
 failure in ventricular hyperten 109 449  
 in poly cythemia 1  
 Myocardial acute interstitial 48  
   suppurative 40  
   differentiated from myxedema 9-8  
   in mumps 90  
   in rheumatic fever 48 400  
   in scarlet fever 11  
   in trichinosis 40  
   pathological anatomy 401  
   syphilitic 40  
   trichinella spiralis 400  
   tuberculous 40  
 Myocardium 401 See also Myocarditis  
   alloy cardiac disease 2 0

Mycotic infection in chronic pneumonia

Myopathic atrophy & e Dystrophic atrophy  
large pr over 10 muscular 1045

M3o illi chronica 1.30  
 a Antich 1.30  
 fibrosa 1.30  
 in a ute follicular ton illi 1  
 in el r nic parana al sit u illi  
 in influenza illi  
 a ton illi 1  
 non upurati e 1 31 1.  
 o a nna progre si a 1 31 1 34  
 priary suppurative 1.30  
 M3o t a i urulentic tropica 1.30  
 M3otonia atrophica 104  
 congenita 164 See Antipolemia congenita

Myotonic dystrophy	9c	Myotonia atrophica
Myxema	9-307	
in cardiac failure	progre	in colge tle

## N

Nais hist phy of 10  
 hereditary arthro pla 1000  
 in idiopathic hypochromic anemia 233  
 in leprosy 1407  
 Naphthol intoxication 79  
 Narcot 14  
 Narcosis in barbiturate poisoning 14  
 Narcosis poisoning 14  
 Nares in diphtheria 83  
 Nasal catarrh chronic differentiated from

factor of bronchitis chronic	150
di change in atrophic rhinitis	148
n hypertrophic rhinitis	
in nasopharyngeal fibroma	3
in paranasal sinuses	4
in tumor of n.s.	6
mucous membranes in i phthia	2
maturation n atrophic rhinitis	3
n hypertrophic rhinitis	

Na oul ar3 ng al le hmantals See Expund a

Na ophar ngit s atarrhai in nfu nza 106  
in pif ic cerebro p nai n en ngitis 106  
in rubella 10

Naopharynx and mouth } ease of 20 40  
specific notation of 30

symptoms 1  
 carcinoma 6  
 fibroma 1 31  
 leiomyoma causing inflammation of 111  
 papilloma 6  
 sarcoma 1 acute anterior poliomyelitis  
 sarcoma 6

rumo 5  
 Nau en 100  
 emotional factors in 1190  
 from aur on 110  
 from streptomycin 14.5  
 in acute catarrhal holangitis 85  
 in chronic patitis 40  
 in food infection 142  
 in infection of kidneys 1.59  
 in malaria 117  
 in Q fever 104  
 in snake bite poisoning 14.50  
 in stomatitis 8

Scapolitan fever & Lindplant fever 693  
Neck stigmas in acute anterior poliomye-  
litis 1091

in epidemic cerebro spinal meningitis 106,  
in influenzal meningitis 10 "

Necrosis acute in chronic cholangitis 0  
chronic stomatitis ulcerati v 44  
in mu tarl gas poisoning 138

Nematodes infection 179  
Neoplasia in bronchiectasis 150  
pelvic malignancy differentiated from pleu

Nephritis acute differentiated from trichinosis

hemorrhagic      See Glomerulonephritis  
acute 16  
chronic anemia in 3

Increased salination in #1  
lehylation #1  
differentiated from Hadebe in Ig lu 69  
differentiated from Hadebe in Ig lu 69

After initial treatment with xeloma 0.6  
 in chronic parotitis 4  
 1 u t t i s fibrosa cystica 0.11  
 0.1 1 2 5

differentiated from beriberi 64  
differentiated from rum 11 ea e 1479  
edema treatment 19

experimental  
in acute follicular tonsillitis and  
rheumatic fever.

in influenza 111  
in mump 90  
in parotitis epidemica 47  
in scarlatina 32

in scarlet fever 3 9  
in septicæmia streptococcus 1 63  
in serum meningitis 10 7  
cultured with art. function 46

reduced all art. functions 40  
treatment 1<sup>st</sup> 1 1 1<sup>st</sup>  
cephal. thal. 1 1 1<sup>st</sup>  
pbr. 1 1<sup>st</sup>

lower nephron 1 241 88  
renal glyco- rja in 47

Nephrosclerosis 149  
Nephrotic state or serous meningitis 107

Ver. 2 cell 9 4-941 1019-10  
 Reflex in 2 female anconophall 108

nervous phenomena in barometric pressure  
system diseases

acute inflammatory diseases 10-3  
Alzheimer's disease 100+

amauro 10 4  
amaurotic family 1100 1039  
anatom 8 4  
anatom of bone 10 10 10

anterior horn cell 943 946  
aphasia 1010  
Argyll Robertson pupil 100  
asthma 627 1041

autonomic system 101<sup>n</sup> 101<sup>r</sup>  
Babinski sign 9-3-2-8  
Bell's palsy 100<sup>r</sup>

Betz cells 47 946  
blood supply 941  
caus. guinea lesion 949

cell 4  
erebellum 343 390  
speech ataxic 140  
cerebral anterior 100 1010

cerebral cortex 100 1010  
cerebrospinal fluid 10 4 1028  
pre-sure comp test bl ck 10<sup>22</sup>  
Chaddock reflex 28

circle of W III 95 96  
conjugate movement parallel 100

(for t) ciliary 90°  
(cond) optic 90°  
(thick) condensation 180°

(third) oculomotor 1000  
(fourth) trochlear 1000  
(fifth) trigeminal 1000  
(sixth) abducens 1000

(s i n) abducens 1909  
(se nth) facial 1907  
(e gi th) auditory 1903  
(n nt) glossopharyngeal 1908

(11th) agus 1000  
(12th) pinal access r 1100  
(twelfth) hypoglo al 1000

## Nervous system diseases —Contd

crossed paralysis 947 1017  
deafness 1003  
degenerative diseases 10 4  
development 931 943  
diagnosis 943  
disturbances of motility 931 999  
dorsal spinocerebellar tract 943  
dysidiadokinesia 930  
dysplasia 103  
dyssynea 329  
hystonia musculorum 99  
encephalitis 1081  
encephalitis (guinea) 1086  
    St Louis type 1084  
encephalography 1041 1079  
endocrine gland relationship 947 1079  
epilepsy 100 1007 1014  
extrapyramidal pathways 991 999  
    abnormal movements 99  
    tonicity 93  
    tremor 99  
eye movements 1000 1001  
facial palsy 1001  
familial constitutional defect 10  
focal epileptic attack 100 1001  
formation of cerebro spinal fluid 10 4  
frontal lobes 1001  
    adversive fluids 1001 1007  
lumina of brain 1002  
hemianopsia 93 1001 1009  
hemiplegia 944 954  
hyperacusis 1007  
in diphtheria 4  
in exophthalmic goiter 911  
in intestinal distention 930  
incoordination 990  
infections 1012  
intention tremor 990 999  
intoxications 1073  
light reflex 1009  
lower motor neurone lesion 944 945 946 947  
macula 1000  
meninges 901  
meningitis tuberculous 10 3  
mental deficiency 1034  
metabolic disease 86  
Mongolian Idiocy 1039  
monoplegia 948  
motility disturbances 934  
neuroglia cell 9 9  
new growths 10 4  
nyctagmus 100 100  
occipital cortex 1004  
Oppenheim reflex 94  
paraplegia 1035  
paralysis in diphtheria 4  
    pre Rolandic cortex 937  
parietal lobe 1008  
pathological diagnosis 1010 1014  
pill rolling tremor 912  
polyomyelitis acute anterior 1030  
polycythemia vera 101  
post Rolandic convulsion 100 1006  
prenatal influence disease 101  
pre Rolandic motor cortex 94 1007 1008  
pyramidal tract 94 94 949  
reflex action 943 944 94 949 1013  
St Louis type encephalitis 1085  
segmental distribution of spinal cord 99 990  
semicircular canals irritation 100  
sensory pathway lesions 937 996  
ornate sensibility 99  
spina bifida 1006  
spinal shock 1018  
stereoscopic vision 1001  
strabismus 1003  
symptomatic 4  
syphilis 100 1001 1018  
    types 100  
tabes dorsalis 100  
temporal lobe 1007  
thiamine chloride deficiency 86  
trauma 10 3  
tuberculous sclerosis 10 9  
tumors 10 4 1123 1126  
    temporal lobe 111  
    x ray 1033  
upper motor neurone center 1001  
    lesion 934 93 986 983  
    paralysis 1018  
vascular lesions 1110 1116

## Nervous system diseases —Contd

Vitchow Robin spaces 941  
x ray examination See Lucephalography and Ventriculography 1031 103  
tension 117  
Nervousness asymptomatic 10  
    uralgia 1145 1140  
    facial 1004  
    sopharyngeal 1006 1140  
    larynx 10  
    pain in 1149  
    po therpetic in herpes zoster 1093  
    sciatitis 1149  
    sphenopalatine 1149  
    symptomatic 90  
    symptom 1144  
    trigeminal 1149  
    trigger zones 1148  
Neurasthenia 73  
    in pellagra 9  
    pain in 3 4  
Neurastitis epidemic See Encephalitis epidemic 1081  
Necrosis 5 1094 1096 See also Hypertrophic interstitial neuritis 1050  
    alcoholic polyneuritis 1034  
    arteric differentiated from beriberi 98  
    bacterial 100  
    diphtheritic 100  
    etiology 1094  
    hypertrophic interstitial 10 0 1000  
    in chronic paranasal sinusitis 9  
    in diabetes mellitus 4 7  
    in finger paronychia 1481  
    in influenza 111  
    in L orskoff's psychosis 1480  
    in tonsillitis 1  
    in typhoid fever 93  
    lead 1095 See also Lead encephalopathy  
    optic in acute disseminated encephalomyelitis 1031  
    in congenital syphilis 1313  
    in mumps 99  
    in uronchitis optica 114  
    in serum disease 1435  
    peripheral 1140 1401  
    in acute ascending flaccid paralysis 1043  
    in diphtheria 4  
    in mumps 4  
    progressive hypertrophic interstitial 10 0 1096  
    retrobulbar in methyl alcohol intoxication 1481  
    in multiple sclerosis 114  
    symptoms 1094  
    treatment 1096  
    vitamin deficiency 1094 109  
Neuroblastoma of suprarenal medulla 94  
Neuroblastomas carotid gland 871  
Neurocirculatory asthenia 3 3 1194  
Neuropathology 117  
Neurophoroma 11133  
Neurophilia 11133  
Neurohumoral mediating mechanism in echo  
    ornate medicine 1169  
Neuromyelia optica 1149  
Neuronitis See Neuritis acute ascending  
    flaccid 1038  
Neuroesophageal See Gastric neurosis 116  
Neurovegetative See Pank disease 1095  
Neurosyphilis 100 1001 1064  
    asymptomatic 10  
    cerebro spinal fluid 1001  
    fever treatment 1063  
    Hirschman reaction 1067  
    Lange reaction positive 10  
    potassium iodide 1064  
    recalculation 1064  
    Wassermann reaction 1063  
    treatment 1067 1064  
    x ray 1064  
    Wassermann reaction 10  
Neutropenia See also Leucopenia 5 7 564  
    566  
    granulocytopenia in 94  
    in paratyphoid fever 147  
    in smallpox 149  
    malignant idiopathic 94  
    sulfonamide in production of 94  
Neovascularization See also Bronchitis 94  
    in bronchi 107  
    symptoms 14  
Neovascularization See also  
    Farr's disease See Fyfe's disease  
    lentiginous angioma 13

Neotlamia le in acute yellow atrophy 44  
Necrotic acid in ratification 141  
Niemann Pick disease also found in  
tissue 58  
amateur the family history 1039  
Night blindness in vitamin A deficiency 4  
Nitric oxide poisoning 1405  
Nitrite reaction in influenza meningitis 10  
Nitrite reaction in arsenic poisoning 1  
Nodding of the heel valvulitis 43  
Nodular circumscribed lipomatous 88  
skin lesions in leprosy 1409  
Nodule esophagus 1346  
fibroid 143  
gummatous in jaw 13  
in glandular 140  
in rheumatoid arthritis 143  
in jaw 1  
Lobomus in bacterial endocarditis 411  
singers 14  
about neonatal  
Noma See also stomatitis gangrenosa 4  
in kala azar 134  
in measles 100  
Nonmalar intermittent fever See Kala azar  
14  
Nocturnal in acute rhinitis 1  
fungus infections 3  
glandular of 3  
leprosy  
lupus of 3 4  
eosinophils 1 4  
specific infection 43  
syphilis 1 4  
tuberculosis  
tumors of 3  
Nucleus of leucocytes in infection  
144  
Numbness in acute 10  
Nutritional deficiencies of 780 88 See also Acro-  
dynamia 94 Amino acids 54  
Beri-beri 8 Hyperlipidemia 8  
806 Ostomy 803 Pellagra 8  
789 Pickets 88 Scurvy 95  
and Sprue 441  
malnutrition chronic 8  
tardiness 40  
vitamin A 44  
vitamin B 4  
vitamin C 4  
vitamin D 40  
vitamin E 504  
vitamin P 40  
Nystagmus 100  
definit on 100  
diagnosis in nervous disease 590  
hypertrophic interstitial neuritis 100  
in Friedrich's ataxia 104  
in hyaline cephalus 11  
in multiple sclerosis 110  
Obeity 483  
metabolic factors in 100  
genetic type in Frohlich's syndrome 507  
in diabetes mellitus 51  
in diabetes of gonads 42  
differentiation of Frohlich's syndrome 43  
epidemic encephalitis 1053  
metabolism in 5  
thyroid therapy 44  
Obstruction of esophagus 80  
foreign body in lung 13  
in bronchus 171  
in bronchiectasis 116  
intestinal 104  
laryngeal 142  
pyloric 4 80  
tracheal 15  
Occlusion of coronary 4  
Occlusion of See Melanoma  
Ocular 85 854  
Oculogyric crises in epidemic encephalitis  
1053  
Ophthalma See Tularemia 1334  
Ophthalmic infections of paratubercular  
stomatitis 34  
Ophthalmic normovolemia in chlorosis 431  
Ophthalmic 48  
cells 48 11

Oligodendrogloma. 11  
 Oliguria 1  
   in acute lea 11  
   in reut n creury poi aing 149  
   in f 1 infections 141  
   in hy lronephro is 1 46  
   in infarcts of the kidney 1 84  
   in nephrosia lower nephron 1 41  
 Onychia in congen tal syphilis 131  
 Opi piori mun p les on 4  
 Ophi alr ia = nococcal 1 31  
 Opi thalmopeg c migra ne 11  
 Opi thoton s 100  
   in African sleeping s ckn s 1 60  
   in epidem ic ce ebro ginal meningitis 100  
   in tetanus 134  
   in tuberculous mening tis 10 3  
 Op un hab t 1451 1454  
 Oppen eim reflex 1 3  
 Oppen eim a d sease see Amyotonia con  
   pen ta 104  
 Optic atrophy See Atrophy optio  
   neuritis n uron velitis optica 114  
 Oral phase psychol cal development 1104  
 Orchitis in gonorrhea 1 3  
   in influenza 111  
   n nump 46  
   in undulant fever 644  
 Organ choice psychosomatic m dione 1100  
 Organic dy function p ycho onatic mel  
   cne 11  
 Oriental sore 1 84 134  
 Orthoma in ci culat ry di eases 31  
   in rheumatic fever 63  
 Ortho tate albumina 1 4  
 Osai s disease See Polycythemia vera 5 1  
 O tel s defo mans 1 1  
   arterio clerous 1 4  
   cardiac failure 1 4  
   ce ebral hemorrhage 1 4  
   different al diagnosis 1 4  
   differentiated fro hyperkerato of the  
   kull 1 4  
   differentated f om multiple myeloma  
   1 08  
   he ed ta y factor 1 3  
   infarcti ns 1 4  
   intermittent claudication 1 4  
   pain n 1 3  
   skeletal ch nses 1 3 1 4  
   synonym 1  
   x ray find r 1  
   ffects of radium 14  
 fibro a cy tica 964 See al o Hyperparathy  
   ro dis 964  
   lyt in 968  
   differentated from dy pia ia fibrou  
   1 0  
   multiple myeloma 1 08  
   osteit s deformans 1 26  
   tr atm nt 96  
   in adlation icke s 14  
   in apyhs 1 14  
 Osteoarthritis 1 49 1 33  
   differentiated f om rheumato d arthrit  
   1 44 1 4  
   spur n 1 0  
 Osteoa throphat hy p trophic 1 D-3  
   n bronchiecta 1 1  
   in ne growth of bronch 168  
   n am b c dy estery 1 0  
 O f o homd ts in congenital phills 131  
 O te gene s mpe fects 1 1 121  
   differentiated from ickets 403  
 O teog nic arcoma eff cts of radium 147  
 O teomalac a 91 804  
   differentated from o te tis deformans 1 0  
   dffe ent al l from rickets 49  
   tetany in 912 404  
   v tamh D d ficency 49  
 O t omelit diff rent at on f om acute  
   rheumatic a thrills 07  
   n diabetic gangren 848  
   n infl uza 111  
   n yph l 1 14  
 Osteopathy See Osteogenes s perfecta  
   1 15  
 O teop tro ia 11 6 11 3  
 Osteoporo l elac dl a e 641  
   enil s dffe ent al d from o teitis lefor  
   mans 1 6  
 Osteo arcoma n o te tis def rmans 1 4  
 Osteo cle = congen tal S e Osteopetrosis  
   1 17

*Ostosclerosia fragilis* & *n. rillata* See *Osteopetrosis* 1 17

Otitis media acute suppurative in rhinitis 7  
in influenza 110 11  
in intracranial abscess 1048  
in lobar pneumonia 104  
in measles 107  
in mumps 90  
in typhoid fever 15  
in whooping cough 17  
syphilitic in congenital syphilis 1 15  
Ovarian in carotid fistula 716  
Ovulation 3  
Oxycephaly See *acrocephaly* 1.27  
Oxygon lecheneys 347  
Oxygon physiology 347  
Oxygon in bronchopneumonia 23  
in chronic pneumonia 11  
in cyanosis 15 15  
of lobar pneumonia 141 15 15  
in emphysema 113  
want medical problem of aviation 1401  
141

Oxyuriasis 703

Ozema 1

Iachymeningitis 951  
Iachymeningitis 107  
intracranial hemorrhage 100  
Paget's disease See *Osteitis deformans* 127  
Pain abdominal 13  
in sciatica 53  
in acute appendicitis 17  
in catarrhal cholangitis 71  
in cholecystitis 71  
in enterocolitis 148  
in hemorrhagic pancreatic necrosis 71  
in lymphocytic meningitis 10 6  
in mononucleosis 140  
in net beriberi 4  
in amoebic dysentery 6 0  
in ankylostomiasis 01  
in bacillary dysentery 13  
in cholera 140  
in chronic cholangitis 7 0  
in coronary atherosclerosis 45  
in disease of large intestine 01  
of small intestine 13  
of stomach 10  
in vertebra 0 0  
in duodenal atony 0 0  
in erythema nodosum 141  
in food infection 140  
in gastric neurosis 107  
in infarction of placenta 1  
in large cell lymphoma 1  
in mucous colitis 1 0  
in nephrolithiasis 1 0  
in peritonitis 491 10  
in regional ileitis 6 8  
in tetanus 10  
in tuberculous peritonitis 10  
in typhoid fever 10  
back in extradural abscess of cord 1080  
in hydrocephalus 107  
in infarction of kidney 1 5  
in kidney infection 100  
in nephrolithiasis 1 0  
in neurasthenia 1 0  
in pyelitis 1 0  
in small intestine 1 0  
in tuberculous infarction of kidney 1 0  
cardiac (retrocardiac)  
ear in lateral sinus thrombosis 1116  
extremities in acrodynia 10  
in acute beriberi 5  
in follicular tonsillitis 1  
in causalgia 1110  
in myxema 11  
in ocellular leprosy 1 4  
in scurvy 97  
facial in acute parotitis 47  
in alveolar abscess 47  
in cavernous sinus thrombosis 1116  
in chronic parotitis 47  
in mumps 9  
in pyramidal sinusitis 4  
in parotitis 47  
in salivary calculi 48  
gastrointestinal emotional factors in 1190  
genital in chloasma 86  
in acute follicular tonsillitis 1  
glander 1340

in general in acute—Cont'd  
rhinitis 21  
spir. chetel hepatitis 3  
in anthrax 1338  
in cholera 676  
in epidemic encephalitis 108  
in influenza 109  
in multiple myeloma 1 06  
in neur. ethica 3 4  
in tetanus fibr. ca. cystic 16  
in Q fever 1361  
in syphilis 1309 1313  
in tuberculous 10 8  
in tetanus 134  
in trichinosis 06  
in tularemia 1335  
in typhus fever 13 7  
in yellow fever 73  
glands (lymph) in chronic tonsillitis 4  
heart in pericardium in acute rheumatic fever 11  
in dermal mycosis 1 31  
in herpes zoster 1401  
in local and systemic herpes 10 0  
in lymphocytic choriomeningitis 1401  
in new growths of bronchi 167  
in snake bite poisoning 1499  
joints in barometric pressure high effect of 14 1  
in gout 1 1 374  
in rheumatic fever 1  
in rheumatoid arthritis 1240  
in undulant fever 693  
laryngeal in larynx of larynx 1 3 1 9  
in tuberculous of larynx 1 9  
limbs lower in sciatica 1149  
upper in cervical rib 1110  
mouth in acute leukemia 3  
in Ludwig's angina 4  
in stomatitis ulcerative 43  
in tuberculous tongue 40  
muscular in tetanus 134  
in dengue 138  
in myelitis ossificans progressiva 1 3  
in nonsuppurative myelitis 1 11  
in papular fever 1383  
in rat bite fever 1347  
in relapsing fever 13 5  
in Rocky Mountain spotted fever 13 7  
in septic arthritis 123  
in spherulitis disease 136  
in trench fever 13 6  
in typhus 14 1  
neuritis in cauda equina 1 10  
in tumors 1125  
in extramedullary tumor 1134  
in herpes zoster 109  
in leprosy 1406  
in neuritis 1024  
in subacute combined degeneration of spinal cord 1138  
new growths of bronchi 167  
ocular in acute lymphocytic meningitis 13 6  
in cavernous sinus thrombosis 1116  
paroxysmal in epidemic pleurodynia 1403  
pleural 491  
in lobar pneumonia 3  
precorial 336  
emotional factors in 1181  
in pericarditis 500  
psychomotor medicine 1181  
retrocardiac in acute rheumatic fever 10  
in coronary arteries 11 1 1 4  
in esophagus 86 89  
upper maxillary region in acute follicular tonsillitis 51  
symptomatic 7  
thoracic in acute maxillary pulpary colic 10  
in aortic aneurysm 115  
in diptheria 57  
in disease of pleura 116  
in Hodgkin's disease 3  
in lobar pneumonia 31 32 39 1  
in new growth bronchi 167  
in respiratory disease 116 11  
in tuberculous of lung 88  
throat in acute pharyngitis 2  
in carcinoma of pharynx 31  
in diptheria 81 85  
in diphtheria 6



I in thro t—Cont'd  
 in t nsilitis 1  
 in tubercul la of pharynx 95  
 in ulcerative tonatiti 42  
 ut nation in g n rhea 13 9  
 Fallor in leaf p nling 1488  
 in uremia 1  
 Palpitation 33  
 in carb n noxite i ion n~ 146  
 v ptonate 10  
 Pal y See also *I m alysis*  
 cranial nerve in c rebral contusion 110  
 in chronic adh lve arachn diti 1078  
 in tub rculous meningitis 1073  
 Lib 1099  
 facial in acute ascending flaccid para y  
 1088  
 n acute parotitis 4  
 Klumpkes 1039  
 Pancrea l ea e of 3 4 See al o *Duct*  
 less glands diseases of and Pan  
 cretitis 4  
 acute hem rhragic pancr atic n cro i  
 3  
 adenoma islands of Langerhans  
 calculi 16  
 diab te m illtu 3 813  
 inte tinal d ge t ve disturbanc s 3  
 stool in 3  
 tumor 7  
 care non a §  
 differentiat i fi n carcinoma of bile  
 duct  
 jaundice in 6  
 an d n B rgh ract n 4  
 Pancreatic d ficiency in sruue 644  
 necro acute i nor hagic in Libet  
 m illtu 81  
 Pancreat ti acute differentiated from ep  
 lomic picurodynia 1404  
 chronic 7 4  
 diab te mclitus 818  
 d fferentiat d fr m choledit a 1 6  
 diff rentiatel fr m mump 96  
 d fferent ated from sruu 644  
 subacute chesiti 81  
 Pan myelotox o s m apla tic an mia 46  
 m benzene poi onng 146  
 Pannicul ti definitio 1 0  
 Panophthalmiti in n castle 101  
 lantopague 10 5  
 Pantothenic a l vitamin B 86  
 Papillidema 99 998  
 cer bi p nal fluid 10 5  
 in p dei ce cerebro p nal nen ng ti 1063  
 in h y lrocephali 11  
 in ntrac an al ab ce 1078  
 tumor s 11 4  
 in subdu al he hage 1103  
 Papill ma horrid plexu 1130  
 la jna 181  
 na pharynx 6  
 Papillat fe er 1388  
 Papul in Oriental e 1 84  
 redd sh n yau 13 5  
 Para an n mzoic ac i fan in B 86  
 Pa a occidionion 18  
 Paraffin ma ste *Pne mon a l po d* 4  
 Paragan licmas q 0 943 944  
 aroid gland 9 1  
 up a enal medulla 943  
 Pa al y a ute a cending flaccid 1088  
 agitan 1117 1119  
 in epi n ic en phaliti 106 1083  
 B own s qua 1 1018  
 bulbar s m also *Progress m bulb pa at*  
 vsi 1146  
 n mump 96  
 proxi m mycula at c i l 1146  
 An l ne e s 1001 1006  
 ero d 98 101  
 l plopia 1001  
 facial n a ut parotit 47  
 n mumps 98  
 family p oie c 1043  
 i ne al of the m ane Se *Pa e i sen al*  
 105  
 nger 1481  
 horoiat al cul motor 987  
 n a ute an r polomy litu 1090  
 d y lrie 8  
 in so ic an u ysm 436  
 n b th tiau a 1098

Paraly i—Cont'd  
 in botulism 1498  
 n c rebral c ntu n 110  
 m dpl the la 5 33  
 in xtrame lullary tu mors 1134  
 n frontal l be tunor 1130  
 in h e litar spa tic yarapleg a 1043  
 in l a i n u ite 109  
 m meningova cular syphil 10 4  
 in multiple myel ma 1 0  
 in neu ti 109  
 in peripheral ne ve trauma 1107 1108  
 in tub dot al 1070  
 infantile See *Foli sigel ti acite an etior*  
 1090  
 I ennt treatn nt, 109  
 laryng al i 1 11  
 n lobar pneun na, 39  
 laryngo v l palat n 101  
 per neal nerve 1109  
 re piratory 1059  
 in acute a cending flaccid paralyti 1087  
 fa tic congenital Se *I fantile ce elial*  
 d plegia 1040  
 n atyotroph c lat al cleros 1146  
 n distu e scler i 108  
 n sel ti 1058  
 upe or la jngeal ner s 119  
 n ptomatic 10  
 third n ve n ep l n c enc phal t 1083  
 va omot r acute m edena f lung 193  
 in lobat pn un n a 41  
 in mu tard gas t i c n n~ 139  
 vocal c i l n ne gro th of b oncl i 16  
 laryngitic fleu alkalo 867  
 la anasal nu ite See *Sin sifis jarana* 47  
 4 6  
 laryphim i in gon rilea 13 9  
 Parapleg a n ap nal cord trauma 1108  
 sia tic 1018 1094  
 hereditary 1043  
 Parale in pected d fferentiated f om car  
 cin m of bile duct 11  
 Int tnal 0  
 Parastic nfe tation 11  
 Pa athormone 960  
 Parathyro i gland 960 966  
 al nomia n tet fbro a cyst ca 966  
 calcium m talolion 960  
 cataract, 964  
 deficiency a ciatic th t tan 1 1  
 hyp parathy o l functi n 960  
 tetany 360 961 964  
 dihydrotachy terol in 964  
 Parathypho d f ver 966 Se al o *Typ'o d*  
 fete  
 B ellus parathypho u 680  
 d fferentiated f in kala a a 1388  
 ti nch fe er 13 6  
 tularemia (typhoid type) 1 3  
 typho d f er 646  
 y n ptomatology 661  
 Par nteral n oculation infectious li ea e  
 1 99  
 Par s general 10 10 8  
 eplep v in 11 0  
 fe er treatent 1063  
 in int st nal di tentio 635 636  
 small bowel d ffe ntia d f omi divet cu  
 lt 661  
 Paresth ia n cauda equ na lcs on tum  
 113  
 in Ja k onian eplep y 11 9  
 n n urit 1094  
 n ubacute comb n l legenerati m of  
 pinal cord 1138  
 m tabes do ali 1058  
 Pa tic zon mult pie a le 1 114  
 Park n onan syndrom See al o *I alysis*  
 agitans 1117  
 and induc a 11  
 n dy tonia mu colorum def r nans 114  
 in ep demic encephaliti 1083  
 n torticollis 1143  
 Parkin on di a e See *Paralysis a i tans*  
 1117  
 Paronychia n calet f v r 6  
 Pa otius acute 46 Se al o *U ips* 94  
 chron c 4  
 ci den c Se *Mu m* 94  
 n influenza 111  
 in lobar pneun n a 40  
 tectic Se *Mu nps* 94

- Iaroxysmal cough in new growth of bronchi 16  
 rhinitis See Hay fever 144  
 rhinorrhea See Hay fever 144  
 ventricular tachycardia 403  
 whooping cough 1 6 1 8  
 Iaroxysms in bronchiectasis 1  
 Iarturition prophylaxis penicillin in 147  
 sulfathiazine in 143  
 role of in immune disease 899  
 Iasteuritis peritis in plague 136  
 Iatchet 1443  
 Iatent ductus arteriosus 4  
 foramen ovale in congestive heart disease 4  
 Iathologic disturbances psychosomatic medicine 1169  
 Iatent treatment of 17  
 Iellosis rheumatica 469  
 Ichitrous Verzbichur disease 1038  
 Ictidra 789 94  
 blood pressure low in 99  
 deficiency of B complex 91  
 diagnosis 793  
 diet in 93  
 differentiated from Addison's disease 936  
 differentiated from erythromelalgia 463  
 differentiated from pruritus 644  
 dioxyphenylamine 91  
 etiology 89  
 gastrointestinal symptoms 9  
 geographical distribution 89  
 infection or parasitic cause 91  
 libido decreased in 9  
 mental symptoms 9  
 niacin deficiency in 786  
 pathological anatomy 92  
 photodynamic cause 91  
 pigmentation 9  
 prognosis 93  
 prophylaxis 93  
 secondary 94  
 symptom 9  
 tachycardia in 9  
 treatment 793  
 urination burning in 9  
 Iemphigus eosinophilic granulocytes 5 9  
 Ienicillin absorption 1493  
 administration method and dosage 14  
 avitaminosis from 14 6  
 bacterial effect 14 1  
 chemotherapy 14 0  
 curative value 1433 1436  
 distribution 14 3  
 excretion 14  
 in actinomycosis 2 0 00  
 in anthrax 1339  
 in bacterial endocarditis 4 1  
 in blastomycosis of lung 318  
 in bronchiectasis 158  
 in bronchitis chronic 149  
 in chickenpox 1400  
 in cholangitis acute 0  
 in diabetic gangrene 849  
 in erysipelas 1507  
 in gliosis acute 37  
 in gonorrhea 1334 143  
 in hepatitis acute spirochetal 36  
 in influenza 113  
 in measles 104  
 in neurosyphilis 1064  
 in parturition prophylaxis 143  
 in pleurisy 496  
 in pneumonia lobar 251  
 in pyelitis 1 91  
 in rat bite fever 1349  
 in relapsing fever 1361  
 in rhinitis acute 1  
 in scarlet fever 8  
 in sinusitis acute 6  
 in smallpox 1498  
 in syphilis 13 1  
 of kidney 129  
 reactions 1323  
 in tonsillitis follicular 9  
 in tsutsugamushi disease 1  
 in tularemia 1337  
 in undulant fever 697  
 in yaws 136  
 serum sickness like reaction 142  
 skin reactions from 14 5  
 solubility 14 3  
 susceptibility of living organisms to 1430  
 Ienicillin—Cont 1  
 therapy preclinical 1491  
 toxic effects 14 4  
 Ienicillinase 14 1  
 Ienicillins of lungs 3 1  
 Ienicillium notatum 14 0  
 Ienis chancre 130  
 Ielefantiasis in gonorrhea venereum 13 8  
 Ienuryal intoxication 39  
 Iepain gastric 686  
 Iytic ulcer 631  
 alkalosis in 86  
 differentiated from cholecystitis acute in inflammation 60  
 cholelithiasis 65  
 chronic hepatitis 749  
 emotional factors 60 119  
 epiphora 89  
 jejunal See Jejunal ulcer 632  
 psychic trauma 607  
 Ierennial cornea See Iasomotor rhinitis 1446  
 Ierforation in apendicitis 6  
 Ieritientia in lymphopathia venereum 13 8  
 Ieriarthritis nodosa 458 460  
 eosinophilia in 4 9  
 vascular lesions nervous system 1112  
 Ieribronchitis caused by mustard gas poison 139  
 in bronchiectasis 1 0  
 Pericardial defect in congestive heart disease 4 1  
 Pericarditis 499 0  
 adhesive 3 9  
 in coronary infarction 44  
 in lobar pneumonia 38 499  
 in rheumatic fever 61 6 499  
 in scarlet fever 6  
 in Salmonella agalactiae infection 609  
 in uremia 499  
 pain 61 500  
 purulent 6 500  
 tuberculous 01  
 Pericardium in acute rheumatic fever 61  
 bulus paradoxus in acute rheumatic fever 61  
 Periclonitis 661  
 differentiated from carcinoma of colon 66  
 Iriduodenitis 634  
 Ieriositis syphilitic differentiated from osteitis deformans 1 6  
 Peripheral circulatory failure 369 3 3  
 neuritis 1480 1490  
 in chronic arsenical poisoning 149  
 Peripleuritis in endocarditis 410  
 Ieritoneal infections acute differentiated from acidosis 833  
 Peritonitis 502 507  
 abdominal rigidity 50  
 cause 50  
 chronic differentiated from chronic hepatitis 49  
 differentiated from acute hemorrhagic pancreatic necrosis 4  
 hiccup in 502  
 in acute cholecystitis 60  
 in appendicitis 6 6 657  
 in epidemic follicular tonsillitis 3  
 in influenza 111  
 in lobar pneumonia 39  
 intestinal obstruction 89  
 leucocytosis 500  
 movable dullness 502  
 pain 491 50 505  
 pneumococcal 603  
 symptoms 50  
 tuberculous fibrotic 505 50  
 x-ray in 502  
 Peritonitis abcess 50 51  
 Perityphilitis See Appendicitis acute 654  
 Peritene 38  
 differentiated from syphilis of the lip 35  
 Pernicious anemia 623 53 545  
 achlorhydria 541  
 blood examination 539  
 bone marrow in 543  
 diagnosis 54  
 differentiated from beriberi 88  
 hyperchromic anemia in cancer of stomach 543  
 in cirrhosis of liver 543

Pernicious anaemia Differentiated from hyperchromic anaemia—Cont'd  
     in dibothrioccephalus latum infestation 543  
     in idiopathic megalorrhoea with megacolon 543  
     hyperchromic macrocytic anaemia of pregnancy 543  
     idiopathic hypochromic anaemia 534  
     leucemia 55  
     sprue 543 644  
     subacute hepatitis 44  
     etiology 41  
     fever in 539  
     hyperbilirubinemia 541  
     lemon-juice tint to skin 37  
     liver extract in 545  
     mouth lesion in 537  
     myeloid hyperplasia in 41  
     leucemia in 541  
     neurologic lesion 54 54  
     pathological anatomy 54  
     prognosis 543  
     subacute combined degeneration of spinal cord 1139  
     symptoms and signs 53 39  
     tongues 53  
     tongue in 539  
     treatment 545  
     van den Bergh reaction  
 Peroneal muscular atrophy 1050  
     nervous paralysis 1109  
     resistant trunk 42  
     Petersen's bacillus in influenza 106  
     Petechiae in epidemic cerebrospinal meningitis 106  
     in scurvy 87  
     in smallpox 1383  
     in subacute bacterial endocarditis 410  
     Petit mal 111  
     Petroleum poisoning 149  
     Petrolium poisoning 149  
     Pfeiffer's bacillus in influenza 106  
     Phallic phase psychological development 1166  
     Pharyngeal tonsil hypertrophy—See Adenoid hypertrophy 31  
     wall bulging in retropharyngeal abscess 9  
     Pharyngitis acute 7  
     in acute rheumatic fever 6 5  
     atrophic 8  
     catarrhal simple 7  
     chronic 9  
     granular—See Pharyngitis hypertrophic  
     hypertrophic  
     of unknown cause  
     Pharynx condition of in diphtheria 83 8  
     diagnosis of 33  
     Pharynx anatomy 56  
     Pheochromocytoma—See Tumors of medulla 343  
     Phenobarbital in epilepsy 115  
     Phenolsulfonphthalein test renal function 61  
     Phimos infected gonorrhea 13 9  
     Phlebitis cause of 195  
     in acute follicular tonsillitis 51  
     in pulmonary infarction 19  
     in scarlet fever 11  
     in thrombophlebitis 466 468  
     in typhoid fever 631  
     venous disease 486  
     Phlebotomy 487  
     Phlebotomy—See Pappataci fever 138  
     Phlegmon gastritis 6 3  
     Phonoturbance of 1 0  
     Pholagen 345  
     Phosphorus catarrh 3  
     Phosphorus 639  
     Photophobia acute leptomenigitis 1065  
     in Rocky Mountain spotted fever 1 57  
     Phrygian 310  
     Phthia acute pneumonia 99 301  
     bronchopneumonia 99  
     lobar form 01  
     pulmonary—See Lung tubercles of 2 8  
     Physical alleys 1451  
     urticaria 141  
     Pianbuba—See Larynx 1324  
     Pick disease 1138  
     Pigment cell 50  
     Pigment cell in Addison's disease 9 5

I mentation—C nt 1  
 in amaurotic family idiocy 1038 1039  
 in ar en s po oning 149  
 in chlorosis 30  
 in chronic arsenical poisoning 149  
 in dysplasia fibrosa 1 0  
 in hemochromatosis (b onze d ab tes) 384  
 in Hodgkin's disease 38  
 in idiopathic strabismus 64  
 in leprosy 1407  
 in neurofibromatosis 113  
 in ochronosis 855  
 in pellagra 9  
 in subacute bacterial endocarditis 411  
 in syphilis 1311  
 in mon yellow tint in pernicious anemia 53  
 P il rolling" tremor in paralytic agitations 1117  
 Pilocarpine hypersecretion 46  
 Pineal gland tumors 966 112  
 Pinealoma 11  
 Pink disease 1095 See also de Odyma 94  
 Pinworm See *Oxyuriasis* 08  
 Pituitary in epilepsy 1153  
 Pituitary adenoma 112 See also Acromegaly 893  
 cachexia See *Cachexia progressiva* 899  
 diabetes mellitus 815  
 gland, diseases of 890 90  
 anatomy 890  
 basophilic 896  
 chromophobe adenoma 90  
 compression syndromes 904  
 craniopharyngioma 904  
 dwarfism 906  
 Erblich's syndrome 89  
 hypopituitary function 898  
 acromegaly 895  
 gigantism 89  
 postinflammatory 89  
 vascular 89  
 hypopituitary function III  
 infantilism 906  
 introduction 890  
 physiology 890  
 Simmonds' disease 899  
 tumor 895  
 hormones 890 891  
 Pituitary 888  
 Placental extracts in measles 103  
 Plague 136 1364  
 Plasmic infection in relation to acute infection 13  
 Plasmodium *alciparum* 13  
 malarial fever 1366 13 3  
 malaric malarial fever 1 66  
 o late 1366  
 latex, malarial fever 1366  
 Pleural diseases of pneumonia 116 11, 490  
 lobar pneumonia 43  
 Pleural effusion 43 493  
 acrophony in 493  
 cyanosis in 136  
 differentiated from new growth bronchitis 1  
 with ascites 49  
 with fibroma of ovary 49  
 friction pneumonia 110  
 in lobar pneumonia 37  
 Pleurisy 43 49, 49  
 cause 43  
 differentiated from cholecystitis acute 60  
 differentiated from lobar pneumonia 43  
 illness 494  
 empyema in 49  
 friction rub 49  
 coccygia 493  
 epidemic follicular tonsillitis 3  
 in Hodgkin's disease 582  
 influenza 110  
 in lobar pneumonia 8 43  
 pneumonia 101  
 in pneumonia 494  
 rheumatic fever 43  
 scarlet fever 6  
 in tuberculous 494  
 in tuberculous empyema 494  
 media thinum of placement 494  
 plastic 49  
 pneumothorax 497  
 pyogenic 496  
 pulmonary infection non-specific 493  
 sulfanilamide in 496  
 symptom 49  
 treatment 496

- Fluoride**—Cent 1  
with effluvia 166 491 492  
x-ray 494
- Fluoritis fibrinosa** in acute rheumatic fever  
6,  
in lobar pneumonia 34  
serofibrinous in acute rheumatic fever 6
- Fluorodysentery** epidemic 1403 1404  
diphtheritic *See* *Fluorodysentery* epi-  
demic 1403
- Fluoropneumonia** *See* *Pneumonia lobar* 6
- Fluoropulmonary tuberculosis** 1338
- Fluoromat** etc 161
- Fluorococci** in bronchopneumonia 14  
in chronic bronchitis 14  
in influenza 106 108 109 110  
in epiglottitis 136  
in septicemia 1302
- Fluorococcal infection** ulcers in 496  
serum tests 0
- Fluorococci** in chronic bronchitis 41  
in chronic bronchitis 14  
in lobar pneumonia 6 7 15  
peritonitis 103  
types of
- Fluorococci** 1 14  
differentiated from chronic bronchitis 148  
differentiated from chronic pneumonia 6  
in chronic pneumonia 261
- Fluoronia catarrhal** *See* *Bronchopneumonia* 14  
croupous *See* *Pneumonia lobar* 76  
cyano in 183  
differentiated from acute massive pulmo-  
nary collapse 04  
chronic fibroplastic pulmonary tuber-  
culosis 86  
plunder 1340  
pulmonary tuberculosis 306  
relapsing fever 1360  
typhus fever 13 3
- Fibrinous** *See* *Pneumonia lobar* 6
- Fibrinolytic** *See* *Fibrinolytic pneumonia*  
73
- in acute parotitis 46  
rheumatic fever 5  
of larynx 46
- in diabetes mellitus 431  
in measles 101 103 104  
in mumps 98  
in pulmonary tuberculosis 103  
in rheumatic fever 1  
in salmonella ulcer infection 69  
in trichinosis 06  
in typhoid fever 135  
in typhoid fever 683  
in whooping cough 1  
influenza differentiated from plague 136  
interstitial *See* *Pneumonia primarum* 140  
causes
- intestinal distention 635
- Lipoid** 4 8
- Lobar** 11 8  
associated with herpes 1 2  
blood culture 41  
bronchiectasis 247  
bronchopneumonia 0 4  
causative agent 6  
chemotherapy in 0  
chloride of zinc of 3 41  
circulatory disturbance in  
course and termination 43  
crisis 13 43  
cyanosis in 103 34 73 51  
delayed resolution 246  
diagnosis 41 13  
differentiated from acute pneumonia  
tuberculosis 1 0 4  
bronchopneumonia 1 0 4  
enlargement 43  
influenza bronchitis 111  
bronchopneumonia 111  
phthisis lobar form 301  
pleurisy 43  
pneumonia in typhoid fever 4  
pulmonary infarction 199  
rheumatic fever pneumonia 1  
dyspnea in 31 3 21  
empyema 39 43 248  
fever in 31  
heart in 41  
hydroxyethylalcohol 0  
in bronchiectasis 10
- Pneumonia lobar**—Cent 1  
in chronic bronchitis 148  
pneumonia 18  
infection general 21  
intoxication 31  
laryngeal paralysis in 39  
leucocytes (other than pneumococcus) 47 13  
leucocytosis 31  
lysis in 13  
manner of onset 31  
massive collapse 236  
metastatic embolism acute 10  
mortality statistical termination 46 48  
mortality 43  
necrosis 146  
onset 31  
otitis media 39  
oxygen therapy 3 4  
pain in 31 3 251 4  
pathological anatomy 30  
penicillin in 1  
pericarditis 39 499  
peritonitis 39  
physical signs 36  
pulmonary friction in 37  
resorption 243  
pleurisy in 38 43  
pneumococcal infections 6 4 4  
0  
pneumothorax 4  
portal entry 8  
preliminary factor 29  
purulent metastasis 39  
Quellung reaction of Weizfeld 8  
rises in 132 37  
respiratory rate in 31 32 23 40  
secondary lesion 38 41  
crum therapy 10  
sputum in 3 36  
streptococcal 41  
ulcers of line 4  
sulfonamides in 0  
symptoms and signs 3  
in signs 6  
treatment 48  
prophylaxis 18  
serum 0  
vaccine 48 49  
typhoid in 40 1 4 0  
types of pneumococci 2 7 45 0  
vaccine therapy 48 49  
x-ray in 31 23 241 4
- Lobar** *See* *Bronchopneumonia* 14  
metastasis in differentiated from epiglottitis  
cerebro spinal meningitis 10 0  
all a pirator *See* *Pneumonia lobar* 4  
primary atypical 4  
ulcers 4  
ulcers *See* *Pneumonia lobar* 6  
Streptococcus in otitis diff. in otitis  
from fibrinolytic pneumonia 4
- Lobar**  
in unilocular disease 6  
tuberculosis acute differentiated from  
lobar pneumonia 47
- Pneumonia acute**  
a pirator in chronic pneumonia 59  
chronic 1  
aspiration pneumonia in 59  
atelectasis 6  
bacteriology 66  
benign tumors of bronchi 9  
bronchogenic carcinoma in 39  
bronchopneumonia in 5  
course 66  
in signs 68  
differentiated from bronchogenic carcinoma  
noma 19  
hyoid pneumonia 276  
pulmonary tuberculosis 1 6 68  
etiology anatomical 6 63  
massive collapse 7  
necrotic infection in 263  
pathological anatomy 66  
physiology 67  
pneumonia in 41  
in unilocular disease 03  
prognosis 63  
pulmonary embolism in 6  
symptoms and signs 5  
phthisis in 62  
treatment 69  
x-ray in  
in planders 1341

Pneum nitis—C ntid  
in influ nza 11  
in n slea 101 104  
metastatic in s ptic-mia 1303  
Pneumonoocci in chronic bronchitis 14  
Pneum opericardium 500  
Pneum opitoneum peritonitis 503  
Pneum orothrax 49;  
acute 186  
artificial 178 54  
in bronchiectasis 159  
in chr nic pneum niti 69 0  
in lobar pneum onia 4  
in pl uri 49  
in tuberculosis of lung 308  
localized differ ntiated from bronchiole  
titic cavities, 163  
prognosis 493  
spontaneous in chronic fibroulcrative pul  
monary tuberculosis 99  
in pulm onary at lectasia 01  
tuberculosis 304  
Pol oning acute differentiated from cholera  
67  
Poker spine ricur atoid arthriti 1 41  
Polioencephalitis in acute anterior poliomye  
litis 1091  
in chick enpox 1400  
Polio nitis acute ante or 1090 1092  
differentiated from paralysis acute  
flaccid 1089  
in acute ascending flaccid paralysis 1089  
lymphocytic in ninitis 10 6  
preparalytic, differentiated from ; epidem c  
cerebro spinal meningiti 10 0  
Poli h fever See Trich fever 13  
Polinoxia See Hys fever 1445  
Polyarteritis See Pe a teritis = dose 4 8  
Polyarthriti different al 3 from acute rheu  
matic fever 68  
in acute rheumatic fe er 6 64 68  
in gonorrh 1330  
in ca let fe er 6  
in undulant fever 693  
rheumatic See Ra u atic feier ac te  
50  
treatn nt of 68 69  
Polycyth mia dil ea = of pulmonary arterie  
489  
in c ngenital heart disease 4 8  
in en phy sia 16 12  
in pulm nary arterie diseases 48  
in iron boang ts obli an 467 468  
v ra 5 5 15 3  
nervous sy ten 5 1 1112  
vascular fe ions nervou ;st m 111  
P lydipia in diab te mellitu 8  
Polymorphonuclear cells, in bronchopne  
monia 719  
P lyneuritis, acute infect ve in acute a cend  
ing fla c d paraly 104  
alcoholic 1094  
to ak ffs psychosi 109  
diabetic 1095  
acute dry be ibe 1 89  
in har akort psychol 1095  
v tamin B defic ency 89  
ith facial dipi 1 1084  
Pcylphagia in diabetes mellitus 8 6 83  
in ga tric neuro 6  
Polypi larynx 131 13  
Polypu s fibromucous d ff rentiated from  
n iopharyng al fibroma, 32  
na al 6  
Polyradicul neur is 1089  
Polysero iti See Sero itis c tr sic adhes ve  
507  
Polyuria 1;  
n diabetes in p d s 868 869  
mellitus 8 4 835  
Fon tumors 113  
Foradenitis See Lymph pathia et veneni  
13  
I tal stasis 71 20  
anastom es 15  
Iositive venous pulsar acute congestive car  
diac fa lure 2;  
I o terolateral sclero s See s bacute cori  
bi ed deg = ai on of pnal  
cv d 1138  
Po ttr um tic d z ne intracranial trauma  
pil p 1153  
headache intracran al trauma 1104

Po ture in di sea e of n rous stem 991  
Potassium in family periodic paralysis 1044  
Pott's disease of spine extradural abscess 1047  
cord in 1050  
I recordial pain 226  
emotional factors in 1181  
Psychosomatic medicine 1181  
Pregnancy cardiac failure 369  
diabetes mellitus 86 827  
hypochromic anemia 524  
renal glycosuria in 569  
thyroid gland 99  
Pyloric fistula 446  
Pernicious dementia See Alzheimer's disease  
1137  
Pericarditis See Eosophagus dysphagia  
Pericardial effusion  
Primary atypical pneumonia  
leishmaniasis  
myopathies See Dysophagia hereditaria  
Progressive bulbar palsy 1146  
lentacular degeneration 104 114  
muscular atrophy 1145  
neural muscular atrophy See Muscular  
atrophy peroneal 1050  
pernicious anemia See Pernicious anemia  
Iron deficiency 1409  
Lymphatic antibiotic and 1431  
cholangitis and 1431  
prooperative penicillin in 143  
sulfonyl urea in 143  
Propulsion paralysis agitans 111  
Prostatic hypertrophy 46  
Protoplasmic myeloma gravis 114  
Prostration in acute rheumatic fever 5  
urinary cholangitis 69  
yellow atrophy of liver 41  
in carbuncle of upper lip 3  
in influenza 109  
in plague 1262  
in radiation sickness 141  
in syphilis case 136  
Protamine insulin test 83  
zinc in ulcers 83  
Protein toxic destruction of 81  
Proteinuria 1  
Protozoan parasitism 11  
Protozoan infestation of intestine 1  
Prune juice prunes 16  
Pruritic neurotic itchy skin 114  
vulvae in diabetes mellitus 86  
Pseudohyperkalemia 841 959  
Pseudoperitonitis muscular 1048  
muscular dystrophy 884  
Pseudoperitonitis in hereditary progressive  
muscular dystrophies 1048  
Pseudoecemia differentiated from lymphoma  
19  
Pseudoclerosis 104  
Pulsation See Pulse 643  
Psittacosis 1 5  
Psychiatric symptoms in epilepsy 1155  
Psychic stimulation diseases of salivary  
gland 46  
Psychological considerations psychomotor  
development, anal phase 116  
genital phase 1166  
oral phase 1164  
phallic phase 1166  
Psychophysiological mechanisms 1166  
phenomena 116  
Psychosis 149  
Psychomotor disorders corticohypothalamic  
sphere 1169  
emotional sphere 1169  
neurohormonal mediating mechanism  
1169  
factors in diabetes mellitus 816  
in neurocirculatory asthma 33  
medication 1161 109 See also Psycho-  
motor  
accidental factor 110  
adrenal cortex, 1200  
angina pectoris 118  
anorexia 1191  
nerve 1191  
appendicitis chronic, 1193  
asthma 119  
behavioral factors 111  
breathing 1191  
cardiac nervous system 1193

- I psychonutritional melline.—Cont 1  
 cardiosperm 1193  
 cardiovascular system 1180  
 cholera 1194  
 colitis mucosa 1196  
 ulcerative 1196  
 congenital factors 1190  
 constipation 119  
 coronary thrombosis 1187  
 cough 118  
 diarrhea 1195  
 dysmenorrhea 1 00  
 dysphonia 1199  
 dyspnea 118  
 dysrhythmia 11 8  
 endocrine system and metabolism 1198  
 gastric neurosis 1191  
 gastrointestinal system 1189  
 tract lower 1194  
 gonads 1900  
 heart diseased 1185  
 murmurs 1183  
 normal emotional effects on 1183  
 hereditary factors 11 0  
 hypertension 118  
 hyperthyroidism 1198  
 hyperventilation 11 8  
 hypotension 1189  
 hypothalamic autonomic mechanism 1169  
 hypothyroidism 1199  
 isotonic factors 11 0  
 indigestion 1191  
 introduction 1181  
 islands of Langerhans 1199  
 locomotor system 1 01  
 nausea 1190  
 neurocirculatory asthenia 1184  
 obesity 1200  
 organ choice 1169  
 pain gastrointestinal 1190  
 precordial 1181  
 pathologic disturbance 1169  
 patient and physician relationship 11 4  
 attitude 11 8  
 peptic ulcer 119  
 physician attitude 11 4  
 psychological considerations 116  
 psychophysiological mechanisms 1168  
 psychotherapy 11  
 respiratory infections recurrent upper  
 system 11 8  
 rheumatism 1 01  
 rheumatoid arthritis 1901  
 rhythm disorders 118  
 sexual disorders 1 00  
 social environment 11 0  
 sublimation 1168  
 symbolic equivalents 11 1  
 systemic vasodilation 11 7  
 tachycardia 118  
 the unconscious 1167  
 therapy general considerations 11  
 practical aspect 11 6  
 thyroid gland 1198  
 tuberculo pulmonary 1180  
 vomiting 1190  
 Psychotherapy 11 5  
 countertransference 11  
 diabetes mellitus 1199  
 dysmenorrhea 1 00  
 endocrine system and metabolism 1198  
 excretion 11 5  
 general consideration 11  
 hypertension 1189  
 locomotor system 1 01  
 obesity 1 00  
 patient and physician relationship 11 4  
 attitude 1173  
 physician attitude 1174  
 practical aspect 11 6  
 rheumatism 1 01  
 rheumatoid arthritis 1 01  
 suppression 11 6  
 systemic considerations 11  
 transference 1174  
 Ptoxis esculenta myasthenia gravis 1143  
 in epidemic encephalitis 1082  
 Pyloric 46  
 in chronic parotitis 4  
 Pubertas praecox in adrenal cortex tumor 941  
 Puberty 940  
 Pulmonary abscess See Lung abscess 16  
 apoplexy 194  
 arteries 484  
 arteriosclerosis chronic 3 9  
 atelectasis 199 62  
 acute massive See Pulmonary collapse  
 acute massive 20  
 cyanosis in 186  
 differentiated from esophagotracheal fistula 87  
 pulmonary infarction 199  
 in acute tracheobronchitis 136  
 in bronchopneumonia 219 1  
 in chronic pneumonia 2 6 266  
 in Friedlin's pneumonia 3  
 in laryngotracheobronchitis acute 137  
 in lobar pneumonia 231 46 48  
 in new growths of bronchi 164  
 in whooping cough 1  
 atresia 4  
 collapse 20  
 acute massive 11  
 cyanosis 186  
 massive in chronic pneumonia 56  
 congestion chronic in chronic bronchitis 14  
 cyanosis 133  
 dilatation See Emphysema 0  
 disease 183 186  
 distention chronic 0  
 dem 186  
 treatment 194  
 embolism 194  
 emphysema See Emphysema 20  
 hemorrhage See Hemorrhages pulmonary 194  
 hypertrophy See Emphysema 20  
 infarction 194 199  
 in essential hypertension 449  
 infections in bronchiectasis 1 0  
 pneumothorax 163  
 emphysema 381  
 in congenital heart disease 4 3  
 hemothorax 194  
 tuberculo See also Lung tuberculosis 78  
 amyloidosis 304  
 atheroma in 303  
 cardiovascular complication 304  
 chlorosis in 31  
 chronic fibroblastic 296 999  
 millary 9  
 classification and course 306  
 clubbing of fingers 304  
 complication 303  
 definition 30  
 diabetes and 331  
 diagnosis 30  
 differential diagnosis 30 306  
 differentiated from bronchiectasis 1 9  
 chronic pneumonia 56 968  
 malaria 30  
 typhoid fever 30  
 emphysema in 303  
 factor in bronchiectasis 14 1 4  
 hypertrophic cartilaginous 1  
 infections in other tissues 304  
 massive collapse 303  
 pleural complication 304  
 pleurisy in 494  
 pneumonia in 303  
 respiratory complications 303  
 silicosis 2 30  
 spontaneous pneumothorax 304  
 treatment 30 313  
 pleurisy 310  
 pneumothorax 308  
 prophylactic 31  
 specific 311  
 thoracoplasty 311  
 x ray in 30  
 Pulse blood pressure 349  
 capillary circulatory diseases 341  
 character in circulatory diseases 340  
 circulatory disease 339  
 collapse 41  
 in arterial aneurysm 443  
 Corrigan 340  
 lent in auricular fibrillation 39  
 diastolic in circulatory disease 340  
 platelet 341  
 postictic in acute congestive cardiac failure 3

Pulse—Cont'd  
   pressure 34  
   rpid in acute rheumatic fever 57  
   rate 339  
   rhythm in circulatory disease 339  
   tenion of 341  
   venous pressure 34  
   volume in circulatory system 240  
     inequality in cervical rib 1110  
   water hammer in circulatory diseases 240  
 Pulvis bigeminus 403  
   paradox in pericarditis 500  
   pericardium in acute rheumatic fever 500  
   tricuspid 403  
 Pupils tonic 100  
   unequal in new growth of bronchi 16  
 Purin group 36  
 Purpura, blood tinea 567  
   caus 567 569  
   chronic hepatic disease 67  
   drug and 56  
   familial senilis in 53  
   bleeding time prolonged 53  
   hemorrhagic vascular lesions nervous  
     system 111  
   Henoch's 569 245  
   idiopathic thrombocytopenic purpura 567  
   in acute rheumatic fever 59  
   in epidemic cerebrospinal meningitis 106  
   in infections 67  
   in influenza 111  
   in valvular rheumatism 69  
   in curv 56  
   in vertebrae 1303  
   in subcutaneous infarction, 6  
   simplex 569  
   thrombocytopenic in chronic meningitis  
     10  
   thrombotic 6  
   vitamin deficiency 67  
 Pyelitis 189  
   differentiated from appendicitis 6  
   in typhoid fever 55  
   symptom and signs 190  
   treatment 191  
 Pyelitis in tumor of kidney 1297  
 Pyelonephritis in typhoid fever 555  
 Pyelonephritis acute differentiated from  
   acute suppurative cholangitis 59  
 Pyemia 1301  
   in epidemic follicular tonsillitis 53  
 Pyemic abscess 38  
 Pyloric obstruction 628 629  
   alkalosis 567  
   extrapyloric lesions 69  
   gastric ulcer 611  
   pyloric condition 69  
   stenosis congenital hypertrophic, 628  
 Pyloric coecum chronic bronchitis 14  
   in 5  
   in scarlet fever abscess 6  
 Pyonephritis in septicemia septic cocci  
   1303  
 Pyonephrosis 195  
   differentiated from tumors of kidney 129  
 Pyopneumothorax in chronic fibrous catarrh  
   pulmonary tuberculosis 99  
 Pyorrhea 41  
   in chronic bronchitis 146  
 Pyranol tract lesion 985 988 See also  
   venous system pyorrhea  
   neurone 1001, 1001  
 Pyrexia, acute catarrhal cholelithiasis 59  
   differential diagnosis pharyngitis 1084  
   Henderson 1340  
   infectious hepatitis 22  
   leptomononucleosis 106  
   mononucleosis 140  
   rheumatic fever 68  
   spirochetal infection 3  
   suppurative cholangitis 69  
   in African sleeping sickness 1390  
   in anthrax 1335  
   in carcinoma of liver 753  
   in chronic arsenical poisoning 149  
   pneumonia 5  
   tonsillitis 54  
   in dengue 1282  
   in epidemic cerebrospinal meningitis 1066  
   pleuropneumonia 1403

Pyrexia—Cont'd  
   in erysipelas 130  
   in foot and mouth disease 1344  
   in infections of kidney 189  
   in infectious meningitis 103  
   in Hodgkin's disease 581  
   in kala azar 1286 1387  
   in lymphopathia venenum 137  
   in malarial fevers 1266 133  
   in miliary tuberculosis 87  
   in non-suppurative myositis 13  
   in pyopneumothorax 1383  
   in plague 136  
   in Q fever 1264  
   in rabies 124  
   in rat bite fever 1247  
   in relapsing fever 139  
   in rheumatoid arthritis 140 144  
   in Rocky Mountain spotted fever 137  
   in epidemic 1362  
   in scarlet fever 1438  
   in smallpox 1393 139  
   in swine fever disease 138  
   in syphilis 1309  
   in syphilitic gummas 750  
   in tetanus 124  
   in trench fever 136 13  
   in tuberculosis of lungs 53 58 9  
   in typhemia 133 1336  
   in typhus fever 13  
   in whooping cough, 16  
   in yaws 13  
   in typhoid fever 37  
   moderate 145  
 Pyroloxine tannin 56  
 Pyrolysis 600  
   necrotic neurosis 67  
   symptomatic 9  
 Pyuria in hydronephrosis 196  
  
 Q  
 Q fever 1264  
 Quackenstedt test cerebrospinal fluid 106  
   103 1081 113  
   in extradural abscess of cerebellum 1081  
   in syringomyelia 113  
 Quellung reaction of Neisseria in lobar  
   pneumonia 8  
 Quinidine in auricular fibrillation 393  
 Quinine hydrochloride in myotonia congenita  
   1047  
 Quins See also Abscess peritonitis 0  
   differentiated from carcinoma of pharynx  
     31  
   in acute leucemia 560  
   in chronic tonsillitis 54  
  
 R  
 Rabies 124 124  
   antirabic inoculation in acute tonsillitis  
     encephalomyelitis 104  
   differs from tetanus 124  
   radiation sickness 1471  
   radiation toxemia 141  
   stimulus effect of 141 143  
   in leucocytosis 141 9  
   Rale atelectasis 133  
   bubbling 133 133  
   in 133 133  
   in acute tracheobronchitis 13  
   in chronic bronchitis 13  
   in disease of bronchi 144 144 105  
   in edema of lung 197  
   in foreign bodies in bronchi 14  
   in lobar pneumonia 133 13  
   in miliary tuberculosis 14  
   in new growths of lungs 140  
   in pleural effusion 401  
   in tuberculosis of lung 14  
   in 144 137  
   mucous 14  
 Radial 40  
 Radial See Erythema  
 Rat bite fever 134 149  
   differentiated from typhus fever 1342  
 Rathke's pouch tumor 904 119  
 Raynaud's disease 412 46, 119  
   differentiated from thromboangiitis obliterans 412  
   malignant 149  
 Reagin in congenital syphilis 1319

- Rectum polyp differentiated from chronic hepatitis 71
- Rel out medical problem of aviation 1401
- Reflex pupillary 100
- stimuli 46
- Reflexes in hydrocephalus 112
- in multiple sclerosis 114
- postural and righting 100
- Regional ileitis 6150
- Regurgitation 50, 40, 51, 607
- Reiter's disease 1249
- Relapsing fever 117, 117a
- arthritis in 1112
- blood examination in 1170
- causes in 117, 117a
- differentiated diagnosis 1170
- differentiated from kala-azar 1158
- malaria fever 117a
- rat bite fever 1179
- trench fever 117
- typhus fever 1111, 1171
- eruptions 1170
- lysis in 117
- pyrexia in 1179
- Spirillum carterii* 1179
- duration 1179
- recurrent 1179
- recurrent 1179
- Spirochaetia recurrentis* 1179
- symptoms and signs 1179
- synonyms 1179
- treatment 1171
- Renal calculus 199
- differentiated from cholelithiasis 6
- tumors of kidney 196
- diabetes See *renal glycosuria* 860
- failure of kidney 196
- function 125, 159 See also Kidneys
- blood chemistry 181
- concentration and dilution tests 199
- excretion of creatinine substance 161
- in acute glomerulonephritis 161
- MacLean's concentration test 160
- Mocenthal test 160
- phenolsulfonphthalein test 161
- two hour test 160
- urea concentration and clearance tests 160
- Van Slyke's urea clearance test 161
- Volhard concentration and dilution test 160
- Renosuria* 160, 160
- infections treatment 161
- chemically 161
- ricket 161
- aceroses 161
- stones caused by uric acid 161
- in osteitis fibrosa cystica 161
- tuberculo is differentiated from tumor of kidney 196
- Renin activator 446
- Respiration amplitude of emotional factor 114
- in epidural hemorrhage 110
- in lobar pneumonia 31, 3, 22a, 40
- trigular 31
- periodic 30
- rapid in acidosis 333
- rate in bronchopneumonia 1, 31, 3
- 23, 740
- in lobar pneumonia 31, 3, 2, 40
- stertorous in barbiturate poisoning 1486
- Retropharyngeal abscess resistance in acute croup 1486
- disturbance in lobar pneumonia 31, 3
- 21
- failure 118
- in mustard gas poisoning 139
- in physicochemical condition 139
- fatigue 119
- infections recurrent upper psychosomatic medicine 1180
- rate emotional factor and 118
- rhythm emotional factor and 118
- system diseases of 111
- cough 116
- causes in 119, 182
- disturbance of phonation 11
- lymphoma in 111
- expectoration 116
- gas poisoning 118
- in acute rheumatic fever 6
- in measles 98, 100
- pain in 116
- Retropharyngeal abscess of cases of—C and
- respiratory disturbances 117, 118
- specific infections 14
- stridor 11
- symptoms of disease 115
- psychosomatic medicine 1178
- tracing in emphysema 12
- tract symptomatic 10
- itching in acute mercury poisoning 149
- Reticulocytes 7
- Reticuloendothelial system 116, 81
- Reticulosis atrophic 6
- differentiated diagnosis 56
- differentiated from agranulocytosis 60
- in leucemia 83
- reticulobulbar neuritis 1147
- methyl alcohol 1181
- multiple sclerosis 1147
- neuromyelitis optica 1143
- retropharyngeal abscess 29
- Rhagades in congenital syphilis 131
- Rheumatic fever acute 70
- arthritis 5
- angina differentiated from lymphoma 88
- Aschoff bodies 56, 5, 8, 9, 61, 64
- cardiac enlargement 56
- leucine treatment 11
- carditis in 69
- clinical signs 69
- chorea in 69, 64, 69
- involuntary in 64
- course of disease 66
- diagnosis 67
- differentiated diagnosis 6
- differentiated from periberl 88
- leucine 1383
- leptomeningitis 143
- diphtheria 58
- gland 1310
- gout 86
- lupus erythematosus disseminatus 141, 1413
- rhumatoid arthritis 146
- rickle cell anemia 44
- trench fever 1306
- trichinella 106
- tuberculous infection 6
- pneumonia in 6
- electrocardiographic changes in 11
- endocarditis 9, 60, 61, 408
- endocarditis lesions of 408
- erythema marginatum in 57
- nodal
- general infection in 5
- hepatitis in 361
- disturbances of rhythm 58
- mitral stenosis 60
- tricuspid valve in 61
- hyperpyrexia in 6
- incubation period 6
- joints in 57
- kidney lesions 64, 65, 61
- myocarditis in 58, 60, 61, 40
- neuropathy in 65
- orthopnea in 11
- pathological anatomy 66
- pericarditis 61, 6, 139, 80
- peripheral vessels in 61
- pleurisy in 19
- in pneumonia 6
- differs from lobar pneumonia 11
- polyarthritis in 68
- portal of entry 6
- prevention of 8
- prophylaxis sulfadiazine in 1431
- purpura in 7, 69
- rash in
- relapse 66
- condary lesion in heart 5
- subcutaneous nodule 64
- symptoms 64
- involuntary
- tachypnea in 60
- tertiary lesions in 66, 69
- treatment 6, 40
- albumin 59, 60, 61, 3, 5
- Rhumatism acute See *Rheumatic fever*
- acute
- emotional factors in 101
- pill 101
- subacute articular 11
- acute 5









Scarlet fever eruption—Cont'd  
 differentiated from measles 105  
 extinction phenomenon 74 80 81  
 exulcate on tonsils in 70  
 general infections in 73  
 hyperpyrexia 74  
 in septic arthritis 1 70  
 incubation period 70  
 inoculation manner of 70  
 irregular forms of 74  
 leucocytosis 3 80  
 mild form 18  
 myocarditis in 18  
 nephritis in 3 10 70  
 pathological anatomy 71  
 pericarditis in 76  
 polyarthritis in 7  
 progressive circulatory failure in 70 3 0  
 prophylaxis sulfonamides in 1432  
 pyogenic lesions in 8  
 relapses and recurrence 70  
 Schultz Charlton extinction phenomenon 74 80 81  
 secondary lesions 3  
 eplic type 18  
 strawberry tongue 74  
 Streptococcus hemolyticus group A 80  
 sulfadiazine treatment 6  
 symptom 70  
 synonym 6  
 synovitis in 8  
 tertiary lesions 9  
 throat in 1 2 6 74  
 toxic type 4  
 treatment 51 67  
 types of 70 9  
 vomiting in 72 74 70  
 scars posttraumatic in epilepsy 11 7  
 Schick test in diphtheria 79 80 81 89 90  
 Schilder's disease 1087  
 Schistosomiasis 710  
 intestinal Schistosoma 10  
 Schistosoma hematobia 710  
 japonicum 710  
 mansoni 710  
 symptoms 710  
 Schizotrypanosomiasis 102  
 Schizotrypanum in Chagas disease 1395  
 Schizotrypanum in trypanosomiasis 1369  
 Schönlein's disease 19  
 Schottmüller's 191  
 Schüller-Christian syndrome See Lipoid granulomatosis 9  
 Schultz Charlton extinction phenomenon in scarlet fever 74 80 81  
 Sciatica 1149  
 differentiated from cauda equina lesion (tumors) 114  
 pain in 1149  
 Sclerosed gait in infantile cerebral diplegia 1040  
 Scleroderma differentiated from gangrenous erythema 1498  
 lupus erythematosus disseminatus 1412  
 Raynaud disease 464  
 in hyperparathyroidism 464  
 in osteitis fibrosa cystica 464  
 Sclerosis diffuse 108  
 in Polizaeu-Mirzabacher disease 1039  
 disseminated 1140  
 in lead poisoning 1140  
 insular 1140  
 multiple See Multiple sclerosis 1140  
 tubero 1039  
 Scleritis in acute anterior polymyositis 1091  
 Scurbutus See Scurvy 95  
 Scotomata 114  
 Scrotal tongue 34  
 Scrub typhus 174  
 Scurvy 67 70 80  
 diagnosis 98  
 diet in 98  
 differentiated from acute rheumatic fever 6  
 differentiated from rickets 803  
 etiology 70  
 hemorrhages in 70  
 hypochromic anemia in 70  
 in serous meningitis 10 7  
 infantile 37  
 pain 97

Scurvy—Cont'd  
 pathological anatomy 98  
 prophylaxis 795  
 purpura in 17  
 skin in 97 78  
 spontaneous hemorrhages 9  
 subclinical forms 98  
 symptoms 97  
 synonym 1  
 treatment 94  
 vitamin C deficiency 1  
 vitamin P deficiency 68  
 x-ray in 98  
 Scurfiness 1403  
 Scurfiness See Oxyuriasis 83  
 Scurfiness congestive See Lupus erythematosus disseminatus 1412  
 Secondary lesion definition 12  
 Secretin 3  
 Secretion rate in rheumatic fever 66  
 Sebaceous arthritis 10  
 Sementia 1138  
 Seizure impairment in neuritis 1004  
 Seizure dental 41  
 Seizure arthritis 136  
 Septicemia 1306 1304  
 in congenital syphilis 1317  
 streptococcal in septic arthritis 1336  
 Serous chronic adhesive 50  
 Serous cavity diseases 482 508  
 chronic adhesive serous 507  
 disturbances of circulation 508  
 tumors 508  
 membranes diseases circulation disturbed 508  
 Siffusion 491  
 bronchi new growth 169  
 chyliform 49  
 chylous 49  
 gold paint 49  
 hemorrhagic 49  
 pain 49  
 tumors 49  
 Serum accidents See Serum shock 1430  
 II case 1437 1439  
 fat low cell disease 641  
 in lobar pneumonia 70  
 shock 14 9 1441  
 sickness 1437  
 sickness like reaction to penicillin 14  
 Sexual development premature in dysplasia fibrosa 10  
 Sexual perturbations in chromophobe adenomata 903  
 in craniohypopharyngioma 905  
 II orders psychosomatic medicine 100  
 Shaking (tall) in paralytic agitation 111  
 Shark fever See Typhoid fever 1335  
 Sharkskin appearance riboflavin deficiency 86  
 Shingle See Herpes zoster 109 1400  
 Shingles fever See Typhoid fever 131  
 Shock 253 30  
 cause of 1-84  
 electric See Electric shock effects 14 4  
 cyanosis in 189  
 in laryngeal obstruction 18  
 in pulmonary infarction 108 140  
 serum 1439 1441  
 treatment of 7  
 Staphylococcus acute See Parotitis acute 48  
 local non pyogenic 4  
 Sickle cell anemia 4 49  
 Scleritis of sclerotic 600  
 Scleritis 1  
 Sighting intermittent emotional factor in 11 9  
 Sigmoid See Intestines large 646  
 Silexosis 71  
 differentiated from pulmonary tuberculosis 10  
 chronic pneumonitis 12  
 pneumonitis 1  
 pulmonary tuberculosis 30  
 Silexosis in case 699 704  
 Simple reflex 973  
 Sings node 14  
 Sings lock 706  
 bradycardia rhythm in the lungs 34  
 tachycardia rhythm disturbance 50  
 Sings 9 91 anal vaccines 1  
 Sings 71  
 acute 6  
 penicillin in 6

- Streptomycin—Cont 1  
 distributed n 14 3  
 exertion 1424  
 1) tamine like reaction 14  
 in acute y llo v str 113 44  
 in bacteric (nloc rdittis 4 1  
 in blastomycosis of lung 318  
 in ch lung (n acute 7 0  
 in colitis (n rative char nle non pcc fle  
 701  
 in diabetic k n rene 349  
 in Frl ill no r pneumonia 4  
 in influenza 113  
 in influenza meningit 10 3  
 in pleur y 496  
 in pyelitis 91  
 in sinusitis cute 6  
 in tubercu si of pharynx, 9  
 pulmonary 312  
 in tubercu u meningit 10 4  
 in tularemia 1337  
 in typhoid fever 689  
 in undulant fever 69  
 secondary reaction 14 6  
 solubility, 14 3  
 susceptibility of living org nle to 1431  
 therapy, proteolytic 14  
 toxic effects 1424 14  
 Streptothricin (n in therapy 1420  
 Streptothricin in lung 3 1  
 Stidor congestional 121  
 definition 115  
 emotional factors in 11 8  
 in respiratory system dis a 11  
 laryngeal 509  
 string sign x ray in mucosa c litis 65  
 Strophanthin in cardiac failure 363  
 Strychnine poisoning differentiated from tet  
 nu 14  
 differentiated from tany 963  
 Stupor episode 1081  
 in uremia 140  
 Subacute combined degeneration of spinal  
 cord 1188  
 pernicious anemia 1139  
 sy pton 1185  
 treatment 1139  
 sclerosi see 8 bacul co b red de  
 generation of f p p at cord 1188  
 Subaortic stenosis in congenital heart dis  
 ease 42  
 Subcutaneous nodule rheumatic fever 64  
 Subdural hematoma See Hemorrhage  
 dural 1108  
 Sublimation n uelo / at o / ed cine 1166  
 Submucosa 14 1  
 artificial respiration n 14 1  
 Sudden death 3 1 3 4 See also Cardiac a  
 est  
 anesthetic 353  
 chemical cause 351  
 cyanide 146  
 n ar nle poisoning 12 3  
 in beritery 88  
 in cardiac lesion 3 1  
 in cerebral arter s dis a 481  
 n coronary arterie dis a 4 9  
 in electric shock 14 4  
 in electrocution 351  
 in heart failure auricular flutter 393  
 in lightning shock, 351  
 in miagra, 92  
 n periarthritis nodo a 460  
 in pulmon y infarct n 198  
 lesions 353  
 in serum shock 1140  
 n syphilis 1223  
 in v ntricular fibrillation 1 1  
 n ous cau e 3 1  
 rupture of heart 353  
 tatu thy ncolymphatic 969  
 Suffocation symptomatic 10  
 Suffocati n catarrh cyanosis in 184 186  
 ga 142 143  
 Supp stifer 692  
 Sulfadiazine chemotherap 14 8  
 in erythrococcus f lung 319  
 in erysipelas 130  
 in gonorrhea 1233 1234  
 n influenza meningit 1073  
 n lobar pneumonia 2 1  
 n paratubercular pharyngitis 1422  
 n plague 1364  
 n rheumatic fever 1431  
 Sulfiazin—Cont d  
 in Salinella ulpe after infection 69  
 in scarlet fever 8  
 in streptococcus meningitis 10  
 sore throat 142  
 in whooping cough 1 9  
 su ceptibility of living organisms to 1430  
 Sulfaguanidine absorption 14  
 chemotherap 14 0  
 in bacillary dysentery 64  
 in ulcerative colitis 01  
 solubility 14  
 susceptibility of living organisms to 1430  
 Sulfanilamide absorption 14  
 Sulfapyridine chemotherapy 1420  
 in lobar pneumonia 0  
 Sulfarep enamine in congenital syphilis 13 1  
 Sulfasuxidine in dysentery bacillary 6 5  
 Sulfathalidine in dysentery bacillary 6  
 Sulfathiazole chemotherapy 14 8  
 in follicular tonsillitis 5  
 in gonorrhea 1234  
 in influenza meningit 10 3  
 Sulfonamides acetylation 14 3  
 administration method and dosage 14 6  
 agranulocytosis from 14  
 vitaminosis from 14 6  
 bacterial effect 14 0  
 cause of aplastic anemia 46  
 of nephrolithiasis 1 93  
 chemotherap 14 0  
 curative value 1433 1436  
 distribution 14 2  
 excretion 14 2  
 fever from 14 4  
 hematology changes from 14  
 n actinomycosis 09  
 in biologic systems of lung 318  
 in bronchiectasis 159  
 n brucellosis chronic 149  
 in chick pox 1400  
 in cholangitis acute 0  
 n rylis 130  
 in Friedlander pneumonia 4  
 in gastritis acute suppurative 6 4  
 in gonorrhea 142  
 in influenza 113  
 in lobar pneumonia 0  
 in picuris 496  
 n production of neutropenia 64  
 in prophylaxis 143  
 n pulmonary tuberculosis 312  
 in pneumonia associated with measles 104  
 n renal infection 1 91  
 in rhumatic fever acute 68  
 in rinitis acute 1  
 in scarlet fever 82 143  
 n sinusitis acute 6  
 in smallpox 1398  
 in toxoplasmosis 1410  
 in tularemia 133  
 in typhoid fever 689  
 in undulant fever 697  
 renal stones from 14 8  
 skin rashes from 14 4  
 solubility 14  
 therapy, prerequisites for 14 1  
 toxic effects 14 4  
 Sulfur dioxide poisoning 1468  
 Sun stroke 1455  
 Suppression psychotherapy 11 6  
 Suprarenal glands diseases of 930 944  
 cortical tumors 941  
 exhaustion and 933  
 hyperfunction of 941  
 hyperadrenal function 940  
 hypoadrenal function 933  
 introduction 930  
 tumors cortical 941  
 medulla 940 942  
 treatment 942 944  
 Surgical operations upon diabetic 857  
 Swallowing difficulties in See Dysphagia 34  
 Sweating in acute rheumatic fever 5  
 in laryngismus stridulus 1 1  
 n relapsing fever 1360  
 night in tuberculosis of lung 86 297  
 Swelling gland in a uel glo it 37  
 parotitis, 4  
 in chronic parotitis 4  
 in edema of glottis 1 2  
 in epidemic follicular tonsillitis 8  
 in leucemia 5



- Tib** for *lis*—Cont'd  
 pathological anatomy 106  
 prognosis 106  
 reeducation 1064  
 Ronberg's sign 1059  
 synonym 1058  
 trophic disturbance 1060
- Tabopore** 1 1061  
 fever treatment 1063
- Tachycardia auricular fibrillation** 394  
 flutter 391  
 in acrolysis 34  
 in acute hemorrhagic pancreatic necrosis 774  
 in cholera 66  
 in pellagra 79  
 in plague 136  
 in rabies 1345  
 in relapsing fever 1359  
 in Rocky Mountain spotted fever 13  
 in tetanus 1342  
 in trench fever 136  
 in tuberculous infection of lungs 111  
 in typhemia, 1336  
 paroxysmal auricular 389  
 ventricular 403  
 psychomotor medicine 115  
 sinus 336  
 ventricular in acute rheumatic fever 8  
 in coronary arteries disease 46
- Tachypnea** definition 330  
 in influenza 109  
 in lipoid pneumonia 3  
 in lobar pneumonia 51  
 in plague 136  
 in rheumatic fever 6  
 in Rocky Mountain spotted fever 17  
 in *Taenia echinococcus* 31
- Taeniasis** *Taenia saginata* 06  
 solium 06  
 Talipes in acute anterior poliomyelitis 1091  
 Tapeworm beef See *Taenia saginata* 06  
 cats and dogs dipylidiosis 79  
 fish See *Dipyl bothrios* 08  
 pork trichinosis 70a  
 rat See *Hymenophorus* 0  
 Tay Sachs disease See *Amegakaryocytosis*
- Tet** diseases of 41  
 Tetani cataplexis spider in subacute hepatitis 744
- Tenesmus** in amoebic dysentery 60
- Tentorium** 221
- Teratomata** 160
- Tertiary syphilis** infection 12
- Tet breakfast** 602
- Tetanus** 1341 1343  
 climate incidence 141  
 clonic spasm 134  
 Clostridium tetani 1341 134  
 death from 134 1343  
 differential diagnosis 1342  
 differentiated from rabies 1346  
 tetanus 463  
 etiology 141  
 hyperelectric stage 1349  
 in acute disseminated encephalomyelitis 1034  
 in smallpox 1398  
 incubation period 1341  
 lockjaw (synonym) 1341  
 pathological anatomy 134  
 portal of entry 1341  
 ophthalmia 1343  
 symptoms and signs 1341  
 synonyms 1341  
 terminal stage 134  
 tetanic antitoxin serum 1343  
 tetanosis 1312  
 tetanoparalysis in 134  
 tonic spasm 134  
 treatment 1343  
 wounds in 141
- Tetany** 960 961 966  
 alkaline phosphate 964  
 alkali 963  
 Chvostek's sign 963  
 differential diagnosis 963  
 differentiated from tetanus 134  
 Erb's sign 963  
 etiology 961  
 in epilepsy 1153  
 in infant 964  
 in rickets 302
- Tetany**—Cont'd  
 in uremia 11  
 infantile (rickets) 364  
 laryngismus stridulus 10  
 low blood calcium 963  
 osteomalacia 964  
 parathyroid 963  
 treatment 963  
 Trousseau's sign 963  
 Tetralogy of Fallot 43  
 Texas tick fever 1364  
 Thalamus tumors 113  
 Thermal sensitivity in patient in syringe mylia 1136  
 Thiamine chloride vitamin B 36  
 deficiency in beriberi 37  
 in acute yellow atrophy 44  
 Thioracil in cancer treatment 91  
 Thioarea in goiter treatment 921  
 Thirst in diabetes mellitus 569  
 in 1111  
 in malarial fever 1373  
 in rabies 1345  
 symptomatic 9  
 Thomsen's disease See *Myotonia congenita* 1047  
 Thoracoplasty in pulmonary tuberculosis 311  
 Thorotrast injections 1033  
 Throat, burning sensation in serum sickness 2440  
 dryness in atrophic laryngitis 28  
 irritation in hypertrophic pharyngitis 7  
 septic scarlet fever 8  
 streptococcal differentiated from smallpox 1396
- Thromboangitis obliterans** 466 460  
 blood cholesterol lowered 467  
 course in 468  
 diagnosis 468  
 etiology 466  
 gangrene 467 468  
 gangrenous ergotism 1398  
 intermittent claudication 466  
 pathological anatomy 467  
 phlebitis 466 468  
 polycythemia in 46 468  
 prognosis 468  
 symptoms 466  
 treatment 468
- Thromboarthritis in trichinosis** 06  
 Thrombocytopenia 5 = also *Essential thrombocytopenia* 01  
 in benzene poisoning 1468  
 in kala azar 1387  
 in lupus erythematosus disseminatus 141  
 in smallpox 139
- Thrombopathy constitutional** See *Purpura familial* 53
- Thrombophilia** essential 354  
 Thrombophlebitis 466  
 in epidemic follicular tonsillitis 53  
 in trichinosis 06  
 in typhoid fever 68  
 thromboses arterial in typhus fever 133  
 Thrombosis See also *Thrombotic thrombocytopenia* 1116  
 arterial 3  
 cavernous sinus 1116  
 cerebral = diabetes mellitus 89  
 in serous meningitis 107  
 in sickle cell anemia 547  
 chronic portal differentiated from chronic hepatitis 743  
 in chronic hyperemia 132  
 in typhoid fever 68  
 late atonism 1116  
 pulmonary See *Pulmonary infarction* 194  
 superior longitudinal sinus 1116  
 sinus 196 3  
 sinus 1116
- Thrush** 34
- Thymus gland disease** 967  
 enlarged differentiated from neoplasms of bronchi 10 171  
 pulmonary tumor 10  
 in myasthenia gravis 114  
 pathological anatomy 967  
 tumor 967  
 Thymusitis in mumps 96  
 Thyroid gland disease of 908 900 See also *Goiter* 908 911 913  
 carcinoma 12  
 radioactivity in 99

- Swelling gland—Cont d  
 in mumps 9  
 in salivary calculi 48  
 in Ludwig's angina 4  
 in suffocative case 14  
 symptomatic 8
- Swift Lillis method neurosyphilis 1063
- Swift's disease See *Aerodysia* 794
- Swineherd's disease 1365
- Sydenham's chorea 62
- Symbole (equivalents) psychosomatic medicine 111
- Sympathin 1014
- Symptomatology 10  
 gastrointestinal tract 9  
 genitourinary system 10  
 nervous system 9  
 respiratory tract 10
- Syncepal attacks in valvulitis 383
- Syndrome adaptation 1900  
 hepatorenal 188  
 tubovascular 184
- Syrovitis scarlatinal See *Scarlet fever* 16
- Syphilides secondary differentiated from ru  
 bella 105
- Syphilis 1307 13 4  
 acute treatment 13 8  
 agranulocytosis 13 3  
 alopecia in 1311 131  
 aplastic anemia in 13 3  
 arsenic in 1321  
 poisoning 132  
 bi mouth in 13 1  
 blindness 13 3  
 blood vessel reaction 1316  
 bone lesions 1314  
 bronchi differentiated from new growths of  
 bronchi 171  
 bullae leion 1317  
 carliac 483  
 cardiovascular treatment 13 4  
 chancre redux 1309  
 Charcot's joint 131  
 condylomata 131  
 congenital 1316  
 agranulocytosis 13 3  
 aplastic anemia 131  
 blindness 13 3  
 cheilitis diffusa 131  
 dermatitis 131  
 differentiated from rickets 803  
 hepatitis 1318 132  
 Hutchinson's teeth 1317  
 hydrocephalus in 1318  
 Jarisch Herxheimer reaction 13 2  
 latent reaction 1319  
 nasal discharge 131  
 nervous system 106 1318  
 nitritoid crisis 13  
 osteochondritis 1317  
 rashes 1317  
 reagin in 1319  
 rhagades 1317  
 septicemia in 1317  
 ruffles 1317  
 splenomegaly 1317  
 sudden death 1323  
 symptoms and signs 131  
 treatment 13 4  
 Treponema pallidum 1317  
 Wassermann reaction 131 1319  
 dermatitis in 13 2  
 diagnosis 1318  
 differentiated from beriberi 188  
 glands 1340  
 gonorrhea 1308  
 Hodgkin's disease 583  
 leprosy 1408  
 lymphopathia venereum 1308 1328  
 plague 1363  
 drugs reaction in 132  
 endocardium lesions 408  
 eruption in 1309 1311  
 etiology 1307  
 gumma 8 131 50 131 1314  
 headaches in 1313  
 hepatitis in 1322  
 in aneurysm of aorta 43  
 in bronchiectasis 150  
 in cardiac failure progressive congestive  
 356 358  
 in chronic parotitis 47  
 in myelitis 1088  
 in valvulitis 3 8
- Syphilis—Cont d  
 incubation period 1309  
 Jarisch Herxheimer reaction 13 2  
 jaundice in 1309  
 Kahn reaction 1319  
 kidney 1 90  
 larynx 130  
 differentiated from tuberculosis of larynx  
 1 9 131  
 lip, chancre 37  
 differntiated from p. ritchie 30  
 liver See *Liver syphilis* 0 1317  
 lues venerea 1307  
 lungs 313  
 meningovascular  
 syphilis 10 3  
 mercury 1 1 13 3  
 mouth differentiated from ulcerative stoma  
 titis 44  
 mucous patches in 1310 131  
 nasopharynx 13 2  
 nephrosis 1 90  
 nervous system in 1051 1315  
 nitritoid crisis 13 2  
 of colon 00  
 o testis in 1314  
 osteomyelitis in 1314  
 pain bones in 1313  
 pancreas in diabetes mellitus 814  
 pathological anatomy 1308  
 penicillin reaction to 1321 1323  
 pharynx 8  
 differentiated from lupus pharynx 9  
 mucous patch 28 9  
 pigmentation 1311  
 potassium iodide 13 1 13  
 primary lesions 1308  
 prophylaxis 13 0  
 pulmonary in chronic pneumonitis 6  
 pustular syphilide 1312  
 rabbit skin, 1314  
 salivary glands 47  
 secondary lesions 1308  
 spinal fluid reactions 1319  
 splenomegaly 1309  
 stomach 618  
 sudden death 13 3  
 symptoms and signs 1309 1313  
 synonym 1307  
 teeth deformity 1317 1318  
 tertiary differentiated from typhoid fever  
 686  
 lesion 1308 1313  
 tongue chancre 39  
 differentiated from epithelioma tongue  
 40  
 tuberculosis of tongue 39  
 mucous patches 39  
 toxic symptom 13 8  
 transmission of 1307  
 treatment 13 0  
 Treponema pallidum 1307 1313  
 treponemacides 1321 13  
 tubercular syphilis 131  
 ulcers in 1314  
 Wassermann reactions 131 1319 13 3  
 syphilitic carliac disease 483  
 gastritis diffusa 61  
 pondyitis 1314  
 ulcers of stomach 61  
 Syringobulbia 1136  
 Syringomyelia etiology 1136  
 in cord trauma 1107  
 in leprosy 1407 1408  
 in syphilis 1315  
 symptoms 1136  
 treatment 1137
- Systemic considerations psychosomatic medicine 117
- T
- Tabardillo See *Typhus fever* 1351
- Tabes dorsalis 1058 106  
 Argyll Robertson pupil 1060 1062  
 ataxia 10 8 1059  
 bladder function 1060  
 cerebrospinal fluid 106  
 cervical tabes 10 8  
 Charcot joint 1060  
 cises 1060  
 fractures 1059 1060  
 lightning pains 1058



Trophodermatoneurosis See *Pink disease* 1035

Trupical sore See *Oriental sore* 1384

typhus 134

Trou cause signs in tetanus 963

Truncus peristalsis of 4

Trypanosoma gambiense in African sleeping sickness 1384 1390

in trypanosomiasis 1389

in trypanosomiasis in African sleeping sickness 1389 1390

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tubercular osteitis 1389

Tumors See also *Neoplasms* in tumors 114

and *Intraspinal tumors* 1134

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31

adenoma 31



- Valvulitis—C at d  
 in rheumatic fever 59 60 61 3  
 in closing of heart 353  
 pulmonary 350  
 regurgitation 2 1  
 signs 350 353  
 stenosis congenital 350  
 sclerotic 3 3  
 synepical attack 53  
 syphilis in 3 5 493  
 tricuspid 350  
 stenosis, 350  
 Van der Hoff reaction 1 1  
 in acute catarrhal cholangitis 68  
 suppurative hepatitis 111  
 in chronic cholangitis 0  
 in obstructive jaundice 11  
 in subacute hepatitis 44  
 Van Slyke's urea clearance test, in renal function 1 61  
 Vaquez's disease See Polycythemia vera 5 1  
 Varicella, 80 1399 See also Chickenpox 1399  
 differentiat 1 from scarlet fever 80  
 molluscum 1396  
 Varicocele in hydrocoele 1 96  
 Varicella 19  
 Varicella, 80 See also Chickenpox 1399  
 differentiated from scarlet fever 80  
 vascular disease arterio sclerotic, 48  
 diseases local peripheral, 460 4 0  
 visceral 4 0 48  
 lesions in cardiac failure progressive congestive 2 8  
 in epilepsy 11 0  
 renal failure 1 6  
 Vasomotor collapse in diphtheria, 3 58  
 instability in menopause 9 6  
 in mucous colitis 6  
 rhinitis 1446 See also Hay fever 144  
 Vasoparalysis in acute yellow atrophy of liver 43  
 Vagrelative neurosis 109  
 Vain dilated chyle in thymus gland tumors 96  
 Vasa 1 48 48  
 peripheral embolic infarctions 196  
 Vascular circulation 430  
 pressure 358 480  
 sinus thrombosis 1116  
 cavernous sinus 1116  
 lateral sinus 1116  
 superior longitudinal sinus, 1116  
 symptoms 1116  
 Ventricles aneurysm, in coronary arteries, disease 4 6  
 Ventricular fibrillation 2 1 404 14 4  
 premature contraction, 400  
 puncture 10  
 Ventriculography 1031  
 Vertebrae, lower lumbar anomalies sciatica, 1149  
 Vertigo 100  
 in plague 136  
 Vibration sensibility loss of in subacute combined degeneration of spinal cord 1139  
 Vibrio comma in cholera 6 6  
 Vincent's angina, 9 See also Stomatitis ulcero 4  
 differentiated from diphtheria 111  
 scarlet fever 9  
 pirillum in acute ulceration of larynx, 12  
 in bacillæmia 1 0 1 1 1  
 in chronic bronchitis 14 143  
 tonsillitis 4  
 in scarlet fever 81  
 in ulcerative stomatitis 43  
 Vinson and Illuminer's syndrome 333  
 Viscous Robin pace 981  
 Virus filtrable 11 36 13 1383  
 in acute rhinitis 0  
 in influenza 106  
 in measles 97  
 in mumps 94  
 in rubella 104  
 pneumonia, See Pneumonia in varicella 1 2  
 Visceral Leishmaniasis See Kala-azar 1386  
 Vision, disturbance of in B tulum 1498  
 in chronic glomerulonephritis 1 69  
 in uremia 1 0  
 Visual phenomena in migraine 11  
 Vitamin B in relation to intestinal absorption 640  
 deficiency 16 1094 1095 See also Autism 84  
 in cardiac failure progressive congestive 3  
 in neuritis 1094 109  
 Vitamin A 34  
 in perleche 3  
 night blindness 1  
 Vitamin B 5  
 in diabetes mellitus 8  
 in peripheral neuritis 1450  
 ubiquinol type 89  
 Vitamin C in scurvy 9  
 Vitamin D dental caries 41  
 in osteomalacia 804  
 in rickets 99  
 Vitamin K, 504  
 in infants 80  
 Vocal cord paralysis tumors of bronchi 16  
 Volar's test in renal function 1250  
 Volvulus See Trench fever 1355  
 Vomiting 600  
 causes of 601  
 emotional factors 1190  
 from aureomycin 14 1  
 in acidosis 523 56  
 in acrocephaly 1 8  
 in acute catarrhal cholangitis 68  
 in cholelithiasis 5  
 in cholelithiasis 1084  
 in emaciated nuchal myelitis 1084  
 follicular tonsillitis 1  
 glands 1340  
 infectious hepatitis 2  
 leptomeningitis 106  
 lymphocytic meningitis 10 6  
 mercury poisoning 149  
 yellow atrophy of liver 41  
 in Addison's disease 33  
 in carcinoma of stomach 619  
 in cholelithiasis 6  
 in chorea, 6  
 in chronic hepatitis 46  
 in craniohypophysealoma 904  
 in diphtheria, 84  
 in duodenal stenosis 63  
 in encephalitis St Louis type 1084  
 in epileptic encephalitis, 108  
 in food infections, 149  
 in foot and mouth disease 1344  
 in gastric neurosis 6  
 ulcer 609 611  
 in infection of kidney, 1 89  
 in influenza meningitis 10  
 in intestinal distention, 636  
 in intracranial abscess 1078  
 tumors 11 4  
 in lymphocytic chorion meningitis 1401  
 in migraines 11  
 in motion sickness 1469  
 in nephrotic low nephron, 198  
 in nephrotic syndrome treatment, 1 80  
 in Q fever 1364  
 in scarlet fever 8 9  
 in snake bite poisoning 1499  
 in stomatitis 34  
 in tetanus 961  
 in tonsillitis, 1  
 in tuberculous meningitis, 10 3  
 in uremia 1  
 in whooping cough 1 9  
 in yellow fever 3  
 symptomatic 9  
 von Barquet test in tuberculosis of lung 51  
 3  
 von Recklinghausen's disease 964 113 6 6  
 al of neuromatosis 113  
 Vulva in diphtheria 111  
 Vulvitis atrophic, vitamin A deficiency 8  
 W  
 Wernicke's reaction asymmetric neurophylis 10  
 congenital syphilis 1317  
 in lupus erythematosus disseminatus 1413  
 in tuberculosis of larynx 1 0  
 in rhinogonovascular syphilis 10 4  
 paresis general, 10 6  
 Water poisoning 14 0  
 Waterbury 600

- Typhoid fever differentiated from—Cont'd  
 typhus fever 1351  
 undulant fever 686 68 69  
 gallbladder infection 759  
 gastrointestinal disturbances 685 689  
 hemorrhage 689  
 in acute parotitis 46  
 leucopenia in 680 681  
 melenia in 68  
 mouth lesions in 68  
 nervous system in 683  
 onset 681  
 parotitis acute 46  
 pathological anatomy 684  
 perforation 69  
 phlebotitis in 691  
 pneumonia 42 683  
 prognosis 68  
 prophylaxis 68  
 respiratory system 683  
 rose spots 681  
 secondary lesions 691  
 spleen enlarged 681  
 stools in culture 69  
 symptomatology 681  
 thrombophlebitis 68  
 treatment 68  
 tympititis 68  
 urine in 681  
 vaccines 688
- Typhus exanthematicus See Typhus fever  
 1351  
 fever 1351 1354  
 arterial thromboses in 1353  
 bronchitis in 1353  
 bronchopneumonia in 1353  
 crisis 13 1351 135  
 differential diagnosis 1351 1353  
 differentiated from relapsing fever 1360  
 Rocky Mountain fever 1358  
 trench fever 13 6  
 eruption 135  
 in acute parotitis 46  
 incubation period 1359  
 nervous system 135  
 pathological anatomy 135  
 pulmonary lesions 135  
 Rickettsia prowazeki 1351  
 symptoms and signs 135  
 synonyms 1351  
 treatment 1354  
 Weil Felix agglutination 13 3  
 mite borne 1354  
 murine 1352  
 rural 13 4  
 scrub 1354  
 tropical 1354

## U

- Ulcer laryngeal 60  
 gastric 607  
 in chronic glandular 1340  
 in Oriental sore 1354  
 in tularemia 1336  
 jejunal peptic 63  
 marginal 63  
 peptic. See Gastric ulcer 607  
 emotional factors in 119  
 stomach. See Gastric ulcer 60
- Ulcer a pterygoidea 4  
 Ulceration in chronic bronchiectasis 150  
 single in pharynx 8  
 Ulcerative colitis chronic nonspecific 60  
 emotional factors in 119  
 Ulceromembranous angina. See Stomatitis  
 ulcerative 4
- Ulerythema centrifugum 1411  
 Unconsciousness symptom atic 10
- Undulant fever 683 689  
 agglutination test 69  
 anorexia in 693  
 Bacillus abortus 693  
 bacteriology 694  
 blood culture in 69  
 examination 693 69  
 carrier 693 69  
 clinical varieties 694  
 complications 696  
 control of sources in animals 696  
 course 694  
 differential diagnosis 695  
 differentiated from influenza 111

## Undulant fever differentiated from—Cont'd

- kala azar 1388  
 typhoid fever 686  
 epidemiology 695  
 eruptions 693  
 fever in 693  
 incubation period 693  
 joint pains 693  
 lesions 693 694  
 on et. 693  
 pathological anatomy 695  
 polyarthritis in 693  
 prognosis 696  
 prophylaxis 696  
 signs 693  
 symptomatology 693  
 synonyms 693  
 treatment 696
- Urea concentration and clearance tests 1260
- Uremia 1269  
 convulsions 1 71  
 decreased saturation in 46  
 dehydration 46  
 in cholera 6 6  
 pericarditis 499  
 symptoms and signs 12 0  
 twitching treatment of 1 81
- Urethritis in gonorrhea 13 9  
 Uric acid metabolism 8 0  
 in gout 8 0 871
- Urinary retention in tetanus 1342  
 system diseases of 1255 1 9  
 edema 1 5 1 8 1259 1260  
 symptomatology 1 7
- Urination changes in rhythm and volume  
 1257  
 frequency in diabetes mellitus 894  
 in tuberculosis of kidney 1 90  
 symptomatic 10
- Urine absence of chlorides 2 7 241  
 albumin. See Albuminuria 1 7 1 50  
 1 82  
 analysis in myxeloma 9 5  
 Hence Jones protein in multiple myeloma  
 1 4 1208  
 blood in 1 69  
 calcium in in osteitis fibrosa cystica 96  
 casts 1257  
 crush syndrome 1 87  
 examination in acidosis 838  
 in renal glycosuria 861  
 in diabetes mellitus 824  
 pus cells 1257  
 in pyelitis 1 90
- Urobilinogenuria 12  
 Urticaria eosinophilic granulocytes 6 9  
 in physical allergy 14 1  
 in serum disease 1438  
 in serum shock 1440  
 synonym 1444  
 treatment 1444
- Uta. See Aspandua 1386
- Uveo parotid fever 314  
 syndrome 315

## V

- Vaccination acute disseminated encephalitis  
 1084  
 Vaccines in bronchiectasis 158  
 in cholera prophylaxis 677  
 in colitis ulcerata or chronic non specific  
 601  
 in diabetics with pulmonary tuberculosis  
 652  
 in lobar pneumonia 48 249  
 in rabies 134  
 in rhinitis 1  
 in influenza paranasal 91  
 in mumps 1337
- Vaginitis chronic in pelagia 9  
 Vagus nerve die per vaginam plexus 59
- Vai uilis 2 5 381  
 acute 6  
 aortic insufficiency 1 6  
 stenosis 378  
 valvular 45  
 cardiac enlargement 381  
 in aortic failure 359  
 in congenital pulmonary stenosis 350  
 in endocarditis bacterial 419  
 in mitral insufficiency 3 8  
 stenosis 378



Water hammer pulse 340  
 Watrous E. L. Richter's an. 433  
 Weakness in botulism 1493  
 in chorea 6  
 in diabetes mellitus 8 6  
 in otitis fibrosa cystica 96  
 in suffocative gas 143  
 progress in Addison's disease 33  
 symptomatic 8  
 Wendenky inhibition in myasthenia gravis 1143  
 Weight loss in diabetes mellitus 8 6 83  
 in new growth of bronchi 168  
 in uricemia 1  
 symptomatic 9  
 Well-Felix agglutination in typhus fever 1353  
 reaction 13 3  
 Wells disease See *Hepatitis acute spirochetal* 3  
 Welch's disease See *Thrombocytopenia* 70  
 Werling-Hoffman disease 1046  
 Westphal's disease See *Isendosclerosis* 104  
 Wet brain 1479  
 Whipworm See *Trichocephalasis* 60  
 White lamp 1460  
 Whooping cough 1 4 179  
 age in 1  
 atelectasis in 1 7  
 aura 1 6  
 bronchopneumonia 1 199 2 1  
 cardiac failure in 1  
 causative agent 1 4  
 circulatory failure in 1 7  
 convulsions in 1 19  
 cough in 1 4 1 7  
 diagnosis 17  
 differential diagnosis 127  
 differentiated from common cold 1  
 diphtheria 1 8  
 epidemic cerebrospinal meningitis 10 0  
 influenza 1  
 measles 1 5 1  
 emphysema in 12  
 fever in 1 6  
 hemorrhages in 1  
 in bronchiectasis 1 0 1 3  
 in chronic bronchitis 146 148  
 laryngitis in 128  
 lethargy in 176  
 lymphocytosis in 1 6 177  
 otitis media 1 7  
 paroxysmal aura 1 6  
 duration 1 7 128  
 treatment 1 8 129  
 pathological anatomy 1 5  
 peribronchial adenitis in 12  
 pneumonia in 1  
 predisposing factors 1  
 sulfadiazine treatment 1 9  
 symptoms 125 1 6  
 synonym 124  
 treatment 1 8  
 tuberculo 1 7 81  
 vomiting in 1 9  
 whoop in 1 4 126 1 8  
 Wilson's disease See *Hioyessia lenticularis* 104  
 degeneration 104

Winter cough See *Bronchitis chronic* 115  
 Wool sorter's disease See *Influenza* 1337  
 Worry symptomatic 10  
 Wound diphtheria 86  
 Wilt drop in cell neuritis 1090  
 pal 3 1489  
 in peripheral nerve trauma 1108  
 neuritis 1450  
 Wryneck See *Torticollis* 1147

## X

Xanthochromia in cerebral vascular disease 1117  
 in extradural abscess of cord 1081  
 in intracranial trauma 1103  
 in intrapontine 113  
 Xanthoma diabeticorum diabetes mellitus 834  
 X-ray effects of 14 1 14 3  
 examination of nervous system 1098 10  
 in acute massive pulmonary collapse 204  
 in bronchiectasis 153 15  
 in broncholectatic cavity 163  
 in carcinoma of pharynx 32  
 in chronic fibroclerative pulmonary tuberculosis 36  
 in millary pulmonary tuberculosis 96  
 in pneumonitis 7 68  
 in cases of stomach 611 61 670 6  
 in foreign bodies of bronchi 1  
 in hydrocephalus 11 3  
 in jejunal ulcer 633  
 in leucoplakia buccalis 19  
 in lipid pneumonia 1  
 in lobar pneumonia 31 3 41 4  
 in new growths of bronchi 169  
 in pneumoconiosis 4  
 in pulmonary infarction 198  
 in salivary glands 48  
 in tuberculo 15 of lung 290 93

## Y

Yafren intoxication 29  
 Yaws 13 4 13 4  
 boomerang skin in 13  
 epithelioma in 13  
 gummatous nodules in 13 5  
 parol in 132  
 pathological anatomy 13  
 primary lesion (mother) 1305  
 symptoms and signs 13  
 synonym 1374  
 treatment 13 8  
 Triponema pestenne in 13 4  
 ulcerative lesion in 13 0  
 Wassermann reaction in 13  
 Y-flow breathing ferment 640  
 fever 36 38  
 differentiate from malarial fever 13 5  
 Yellow Jack See *Yellow fever* 38

## Z

Zell-Nissen test tuberculo 1 of lung 10  
 Zonit See *Herpes zoster* 1400

